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THE NATURE OF SHOCK.*

S. J. MELTZER, M.D.
NEW YORK.

In the clinical literature, shock designates a group of grave symptoms which frequently lead to the death of the individual. At the post-mortem examination no anatomic changes can be detected which would account for death and the grave symptoms preceding it. The fatal disturbance underlying the phenomenon of shock is, then, exclusively of a functional nature. From a purely scientific point of view, shock is, therefore, a subject pre-eminently belonging to the domain of pathologic physiology. It should be mentioned that the term shock employed in normal physiology is not identical with the syndrome in which we are interested here. The shock of the physiologists refers to the depression and suppression of spinal reflexes brought about by a direct injury to the cord. We shall not stop here to discuss the possibility of a common ground for both forms of shock. We wish, on the contrary, to point out one strikingly distinguishing feature: physiologic shock is practically not progressive; on the contrary, as a rule, it is fairly rapidly regressive. Clinical shock is, as a rule, progressive, although, as we shall see, it is not invariably fatal.

In selecting the discussion of the nature of clinical shock as the subject of my present address, it is chiefly my intention to record some experimental facts which we obtained in the course of various series of investigations and which may have some bearing on the interpretation of clinical shock.

As an introduction to this report, however, it will be necessary to dwell briefly on the clinical facts of our syndrome and also to review briefly the theories as to the nature of shock now in vogue and the experimental facts on which they are based. As to the clinical picture of shock I could not do better than to quote the description of a concrete case of shock as lucidly given by Fischer[1] nearly forty years ago:

> A strong and perfectly healthy young man was struck in the abdomen by the pole of a carriage drawn by runaway horses. No recognizable injury was done to any of the internal organs. Nevertheless, grave symptoms made their appearance immediately after the accident. The injured man was lying perfectly quiet and paid no attention to anything going on around him. His face was drawn and

* Address delivered at the Academy of Medicine of Toronto, April 7, 1908.

1. Fischer, H.: Samml. klin. Vortr., 1870, No. 10, p. 119.

peculiarly elongated, the forehead wrinkled and the nostrils dilated. His weary, lustreless eyes were deeply sunk in their sockets, half covered by the drooping eyelids and surrounded by broad rings. The pupils were dilated and reacted sluggishly to light. The eyes had a glassy and vacant expression. The skin and the visible mucous membranes had a marblelike pallor. Large drops of sweat hung on forehead and eyebrows. The rectal temperature was subnormal. The sensibility of the entire body was greatly reduced; the patient reacted slightly and only to very painful impressions. No spontaneous movements of any sort were made by the patient. On repeated and urgent requests he showed that he could execute limited, brief movements with his extremities. When the limbs were lifted passively and then let go, they fell down like dead. The sphincters were intact. The urine obtained by catheter was scanty and concentrated, but otherwise normal. The almost imperceptible pulse was rapid, irregular and unequal. The arteries were narrow and of very low tension. The patient answered slowly, reluctantly, and only after repeated urgent questioning. His voice was hoarse and weak, but well articulated. On being repeatedly questioned, the patient complained of cold, faintness and deadness of all parts of the body. When he shut his eyes he felt nauseated and dizzy. The respirations appeared irregular; long, abnormally deep, sighing inspirations interchanged with rapid and superficial ones, which were scarcely visible or audible.

Recapitulating briefly, the essential symptoms of this typical case of traumatic shock consisted of general profound apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid, small pulse, thready and soft arteries, irregular gasping respirations and subnormal temperature.

Fischer does not state the subsequent fate of that patient.

Shock brought on by a blow on the abdomen has often had a rapidly fatal termination. This is graphically illustrated by the following instances given by Sir Astley Cooper:[2]

A man walking through Fleet street (London) one day, happened to quarrel with a woman, when another man came up and gave him a blow in the region of the stomach, which caused almost instantaneous death. On dissection, no cause could be found to account for his sudden death.

A man belonging to the India House was attempting to lift a weight, when another came up and jocosely said, "Here, stand on one side and let an able man attempt it," and at the same time gave him a slight blow on the stomach, when the poor fellow dropped down and expired. His body, on being opened, showed no marks of violence.

Similar rapid fatal terminations from shock are reported from injuries to the testicles. John Hunter[3] is stated to "have seen a man die almost immediately on the loss of a testicle." Fischer[4] tells that he has seen a strong man dying of shock a few hours after he was bitten in the testicle by a wild horse. However, there are some cases with all the symptoms of profound shock which, nevertheless, recover completely.

2. Cooper, Sir Astley: Lectures on Surgery, 1830, p. 9.
3. Hunter, John, quoted by Morris: Shock, London, 1867, p. 13.
4. Fischer, H.: Samml. klin. Vortr., 1890, No. 10, p. 119.

Travers,[5] who probably was the first surgical author to use the term shock with the precise meaning attached to it now, writes:

> Again and again I have left the bedside of patients brought into the hospital pulseless and apparently moribund without any external injury, having suffered falls or blows so serious as to have induced the symptoms of prostration to an alarming extent, and have found them on the succeeding day, to my great surprise, restored to the tone and tranquility of normal health.

The shock described in the foregoing instances is generally designated as traumatic shock. It is characterized by sudden onset and rapid development of the symptoms following immediately on an injury more or less violently and rapidly executed. In recent literature we frequently meet with the term "surgical shock," which has reference to the condition of shock which develops in the course of a surgical operation or soon after it. It occurs most frequently in abdominal and brain operations. It differs from traumatic shock only in its slower development, although most of the recent writers have dwelt in their description specially on the behavior of the heart and the blood pressure. Possibly the pathologic state preceding the operation, the anesthesia and the loss of blood combine to obscure the sharp outlines of shock as seen in purely traumatic cases.

As to the theories, the earlier writers spoke in a vague way of the central nervous system as being the seat of the affection. Cases of shock produced by mental terror without any physical injury gave support to such a view. It was assumed that a strong emotion, as well as a physical commotion, caused some sort of profound molecular changes in the brain.

The first well-defined theory was brought forward by Fischer,[6] who founded it on the well-known experiments of Goltz. Repeated strokes on the abdomen of a frog causes stand-still of the heart and paralysis of the arteries and the veins of the abdominal cavity, which is brought about by reflex paths. Fischer assumed then that traumatic shock consists of a vasomotor paralysis, especially of the splanchnic area, where the bulk of the body's blood is accumulated, with a consequent anemia in other parts. Shock was a hemorrhage into the body's own large veins. According to Fischer, the vascular disturbance was the primary cause, all other symptoms were secondary phenomena due to the consequent anemia of the peripheral parts.

Another theory was that of Groeningen,[7] who assumed that all the nerve centers were equally affected, not by paralysis, but by exhaustion

5. Travers: Inquiry Concerning Constitutional Irritation, London, 1827.
6. Fischer H.: Samml. klin. Vortr., 1890, No. 10, p. 119.
7. Groeningen, quoted by Warren: Surgical Pathology.

brought on by the traumatic over-stimulation. Mansell Moullin is credited by Warren[8] with the theory that the various nerve centers of the body were not exhausted, but inhibited.

These and some other theories were simply construed at the writing desk of their authors. It is only within the last decade that more or less efficient attempts were made to study the nature of shock by the experimental method. As far as I can see, the experimentation led up only to a study of surgical shock; that is, to a shock which developed gradually, similar to that occurring in surgical practice, and there are no reports of experiments in which shock developed as rapidly as in the traumatic cases.

The most extensive series of experimental work on the problem of shock was carried out by George W. Crile. The protocols of the experiments and the conclusions drawn from them are published in two large monographs.[9] The experiments were made on dogs while under ether anesthesia. The various tissues, like skin, muscle, nerve, bone, etc., in the various parts of the body: head, neck, thorax, abdomen, extremities, etc., were subjected to various strong mechanical irritations, to burning and to electric stimulations, with a view to study their effects on blood pressure and on the production of shock. The effects of these various stimulations on respiration and cardiac activity were also studied but less extensively. The chief facts reported by Crile are as follows:

> Strong irritations, like cutting, tearing, burning the skin all over the body, except over the abdomen and testicles, and of the sensory nerve trunks cause, as a rule, a more or less strong rise of blood pressure during the stimulation. Cutting the skin over the abdomen or over the testicles causes as a rule a fall of blood pressure. Opening the abdomen, exposing and handling the intestines, cause a continuous fall. Repeated stimulation of the skin or nerve trunks leads at first to a diminution in the increase in the rising effect, then comes a stage in which the stimulation causes primarily a fall and finally ends up with a stage in which stimulation has no effect whatsoever on the blood pressure. At that stage usually the blood pressure is very low and can not be permanently improved by any medicinal or other treatment. This is, according to Crile, the stage of complete surgical shock. The development of shock is hastened by the strength of the repeated stimuli and by the amount of tissue involved in the stimulation; under all circumstances, however, its development is always a slow and gradual one.

The characteristic signs of surgical shock are, according to Crile, the very low blood pressure and the impossibility of influencing the pressure by any stimulation. The cause of it is exhaustion, the breakdown of the vasomotor center by the preceding over-stimulation. Adrenalin may

8. Warren, John Collins: Surgical Pathology, 2d ed., 1900.

9. Crile, George W.: An Experimental Inquiry into Surgical Shock, Philadelphia, 1899; also Blood Pressure in Surgery, Philadelphia and London, 1903.

temporarily raise the blood pressure by a contraction of the muscles of the wall of the blood vessels; also transfusion or peripheral mechanical pressure may raise the blood pressure simply by hydraulic principles, but the rise will be only temporary. The pressure will not be self-sustaining on account of the complete exhaustion of the vasomotor center.

According to Crile, then, failure of blood pressure is the primary and sole cause of all the symptoms of shock, and this failure has as its cause solely the exhaustion of the vasomotor center. The cardiac and respiratory failures and other phenomena are only secondary consequences or subsidiary factors to the primary cause, the exhaustion of the vasomotor center.

Crile makes a distinction between shock and collapse. In the latter low blood pressure and all the other symptoms of shock may be present. But the onset of collapse, Crile says, is sudden and the conditions are amenable to stimulation because the vasomotor center is not exhausted, but only depressed and can be raised to activity by stimulation. As far as I can see, the difference between shock and collapse, according to Crile, is as follows:

> The onset is gradual in shock and sudden in collapse. Collapse may have its origin in cardiac, respiratory or vasomotor insufficiencies; shock is of vasomotor origin only. Collapse is amenable to stimulants and stimulation; shock is not. In shock the vasomotor center is exhausted; in collapse, if this center is affected, it is only functionally depressed.

I shall not discuss here whether it may be possible to distinguish at the bedside of a human patient between shock and collapse, although such a distinction might be of practical vital importance, since, according to Crile, stimulants like strychnin or alcohol may hasten the end in shock, but may save life in collapse. I wish only to call attention to the fact that shock as described by Crile fits only surgical shock, and that traumatic shock, especially as was described classically by earlier writers, had, on the contrary, mostly, if not always, a sudden onset. I hardly think that Crile assumes that all these cases were only of the collapse variety. But I could not find in his writings a discussion of this apparent discrepancy.

Crile's results and teachings have been widely accepted in the surgical world, especially in the United States and England. They were endorsed by such prominent experimental surgeons as Victor Horsley and Harvey Cushing. They were given a wide prominence by the lectures of Mummery[10] in England and they have found their way into all new text-books.

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10. Mummery, P. Lockhart: Lancet, 1905, i, p. 696, ff.

Within the last few years, however, some divergent views made their appearance. Boise,[11] in the United States, and Malcolm,[12] in England, who are willing to accept the facts as they are reported by Crile, attempted to interpret them differently. They believe that the low blood pressure and the venous stasis observed in surgical shock need not be due to paralysis of the blood vessels and an exhaustion of the vasomotor center, but, on the contrary, can be and are the outcome of a high stimulation of the center and a strong contraction of the heart and the arteries. The theories of these writers are not supported by any observations or experimental tests of any weight, and we shall not enter into a discussion of the validity of their theoretical arguments.

I shall mention particularly, however, some important experimental work recently done by very competent physiologic investigators. W. H. Howell[13] undertook to produce shock in anesthetized dogs either by prolonged handling of the intestines or by applying heat to a large surface of the skin or by operations on the brain. He was frequently confronted with the experience that what produced shock readily in one animal singularly failed to have any effect on another animal. Howell distinguished two forms of shock, cardiac and vascular. In some cases the pulse would be feeble and very rapid, while the blood pressure would remain of a fairly good height. In other animals the blood pressure would drop to forty or twenty millimeters of mercury, while the pulse would also be greatly accelerated. Cardiac shock could occur without vascular depression, while vascular shock was always accompanied by cardiac shock. Howell thinks that neither the vascular nor cardiac shock was due to an exhaustion of the medullary centers, for in neither case were there any signs of a preceding over-excitation. He assumes that both cases of shock are due to an inhibition of the centers in the medulla, that is, an inhibition of the tonus of the vagus center which causes acceleration of the heart and an inhibition of the vasomotor center which leads to vascular shock.

Howell, then, like Crile, sees in the disturbance of the circulation the essential characteristic of shock, but differs from him in that he does not assume that the vasomotor center is exhausted and that he lets the cardio-inhibitory center share in the causation of the shock.

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11. Boise: Amer. Jour. Obstet., 1907, lv, p. 1.

12. Malcolm: Lancet, Aug. 26, 1905, ii; also Lancet, 1907, i, p. 497.

13. Howell, W. H.: Contributions to Medical Research, dedicated to Victor C. Vaughan, 1903.

The vasomotor studies of W. T. Porter alone and with his pupils[14] led him to results and views entirely antagonistic to those brought forward by Crile. In the first place, in disagreement with Crile, he states that in his numerous experiments he failed to find an instance in which stimulation of an afferent nerve caused a significant fall of blood pressure, except, of course, on stimulation of a depressor nerve. In his experiments, crushing or electric stimulation of the testis always gave a rise and not a fall of the blood pressure. Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning. An analysis of 765 blood pressure records from stimulations of the sciatic and brachial (and depressor) nerves of rabbits, cats and dogs brought out the result that the "percentage change in blood pressure, which is the true index of the condition of the vasomotor cells, increases as the blood pressure falls." Even in experiments where all the clinical signs of shock were present: the blood pressure very low, the temperature subnormal, the heart beat weak and often irregular, and the irritability of the nervous system apparently much reduced, stimulation of the depressor nerve lowered the blood pressure by 45 per cent. All these data, says Porter, are wholly opposed to the hypothesis that exhaustion of the vasomotor center brought on by over-stimulation can be the cause of surgical shock. Porter offers no theory of his own as to the nature of shock, but he is very emphatic in his assertion that the vasomotor cells in shock are neither exhausted, depressed nor inhibited. Porter contradicts Crile's facts and disagrees with his exhaustion theory; but apparently he also disagrees with Howell's views, that inhibition of the vasomotor and cardiac centers are at the bottom of the phenomena of shock.

In connection with this review it may be mentioned that, according to a recent statement of Sollmann[15] and his associates, "corrosion or violent irritation of the gastric mucosa, submucosa and serosa, or of the parietal peritoneum has generally no effect on blood pressure or respiration in anesthetized dogs, the observations extending some time over an hour."

This brief review will suffice to show that the experimental era has not yet solved the mystery of shock, and that the bringing forward of new experimental facts capable of shedding some more light on our puzzling problem is not yet a superfluous luxury. Before beginning the report of our own experimental results I wish to complete the foregoing review by the addition of two brief statements.

14. Porter, W. T.: Am. Jour. Physiol., 1907-'08, xx, pp. 399, 444 and 500.
15. Sollman, Brown and Williams: Am. Jour. Physiol., 1907, xx, p. 74.

Henderson[16] has recently adopted Mosso's theory of acapnia also for the causation of shock. Acapnia means an insufficiency of carbon dioxid in the tissues and fluids of the body, and Mosso believes that this insufficiency is the cause of mountain disease. Henderson believes that the lack of carbon dioxid is also the cause of shock which, for instance, develops in laparotomies on account of the escape of this gas from the exposed peritoneum and intestines.

The other statement has reference to the brief mention of Bainbridge and Parkinson[17] last year of two autopsies of postoperative shock in which the chromaffine tissue of the suprarenals was absent. If such findings should turn out to be the rule, we may soon find a new and plausible theory of the nature of shock. This, however, must be left to the future.

Our experiments which I wish to mention here were not undertaken and carried out with a view of determining the nature of shock. Laparotomies were made on animals under various conditions for the purpose of studying certain problems in connection with the gastrointestinal canal. In these studies, however, some facts came to light which may be of assistance in the elucidation of some of the mysteries of shock, and that is the reason why I wish to report them here.

The first series of experiments deals with the motility of the gastrointestinal canal. We found there the fact that simple opening of the abdomen has a profound influence on this motility. Experimenters open the abdomen as one opens the door of a room to see the doings and hear the conversation which is going on, and they are then surprised that everything is quiet. If the abdomen of a rabbit is open it is found that the bulky organs, the stomach and cecum, which fill up nearly the entire abdominal cavity, are practically without any motion.

The literature, therefore, contains hardly any statement concerning the motility of these organs, especially that of the cecum, which is very large in the rabbit. Dr. Auer and myself[18] have discovered, however, that if a normal rabbit is stretched out on its back and the hair over the abdomen cut the regular movements of the stomach and cecum are very plainly visible; the movements of the cecum are especially coarse and easily visible and palpable. Nevertheless, on opening the abdomen there is not a sign of these movements, which appear to be suppressed by this procedure.

16. Henderson, Yandell: Am. Jour. Physiol., 1908, xxi, p. 126.

17. Bainbridge and Parkinson: Lancet, 1907, i, p. 1269.

18. Meltzer and Auer: Zentralbl. f. Physiol., 1907, xxi, No. 3; Proc. Soc. for Exper. Biol. and Med., 1907, iv, p. 37; also John Auer: Am. Jour. Physiol., 1907, xviii, p. 347.

We then carried out a series of experiments to find out the cause and nature of this suppression. The cecum was studied first. In the beginning we sought to determine whether it is not the pain due to the incision after the animal comes out from the anesthesia which inhibits the movements. For this purpose we have first sectioned the spinal cord at the upper end of the dorsal region. Sooner or later the movements of the cecum were as regular as usual. We could now open the abdomen without causing the animal any pain. But it was found that now, too, there was not a sign of cecal movement. The suppression, then, was not caused by pain. The opening of the abdomen admits air, and sometimes cold air, and it is usually assumed that this has a profound effect on the peritoneum and intestines. We thought that this might be the cause of the suppression of the movements. In testing this surmise we discovered that it was not necessary to open the abdomen; simple free dissection of the skin of the abdomen from the underlying muscles was sufficient to stop these movements. It was then evident that the suppression of the movements was not due to direct action upon the cecum but to some reflex act. Temporary closing of the skin over the wound restored the movements again. That it was not the contact of the skin area with the cold air, or at least that it was not this alone, which caused reflexly the suppression of the movements could be proved by the fact that covering the area with warm physiologic solutions did not restore the movements. A similar result was obtained, though the effect was less strong, when the skin of the thighs was freely dissected. Furthermore, even submerging the posterior part of the animal with the cut cord in a bath of 40 degrees C. stopped the cecal movements for some time. Apparently any adequate stimulus applied to the animal caused by way of reflex to the spinal cord an inhibition of the cecal movements. The dissection of the skin presents such a stimulus, and although we are as yet ignorant as to which of the factors accompanying the dissection is the essential stimulus, we know that the dissection presents a group of abnormal conditions, and any abnormal condition might serve as a stimulus. The assumption that the suppression of the cecal peristalsis is an act of reflex inhibition we have further tested by the complete destruction of the spinal cord. In this case dissection of the skin was incapable of interfering with the cecal peristalsis, which was then even better than before. The evil ghosts of exhaustion and fatigue which for more than half a century cast their dark shadows on many bright ventures in physiology could not obscure the issue here. The suppression of cecal peristalsis by dissection of the skin could not have been brought on by overstimulation and exhaustion, since after destruction of the cord and

dissection of the skin the peristalsis was not hampered and in fact was better than before. The mechanism of this reflex inhibition of peristalsis is apparently this. The splanchnic nerves and perhaps also some hypogastric nerve fibers are inhibitory nerves for the gastrointestinal canal, just as the vagus is an inhibitory nerve for the heart. In the normal state an inhibitory tonus is present, that is, cutting of the splanchnic nerves causes an increase of the normal peristalsis. The tonus is probably sustained by continuous mild reflex stimulation from the periphery. When an abnormal, strong stimulus is applied to the periphery, like the dissection of the skin, reflex inhibition becomes increased to such a degree as to completely stop the normal peristalsis. When, however, the cord is destroyed and no spinal reflexes are possible, the dissection has no effect and by the elimination of the normal tonus the normal peristalsis becomes even greater.

Our further experimentation, however, revealed the presence of another inhibitory mechanism. We found that after destruction of the cord there was a sharp difference in the effect between simple dissection of the skin and complete opening of the abdomen. In the latter case the peristalsis, which now did not disappear immediately after the performance of the laparotomy, was not as complete as normally and continued only for a short time. Even in a warm bath of a physiologic solution the cecal peristalsis ceased after ten or fifteen minutes. Since there could be no reflex effect, the early subsidence of the movements must have been accomplished by the stimulation of some peripheral inhibitory mechanism. We did not try to locate the habitat of this mechanism, whether it be in the peripheral ganglia, nerve endings or within the muscle cells of the intestines.

This series of experiments, then, established safely the following conclusions: That simple dissection of the skin over the abdomen presents a distinct stimulus; that this stimulus when the corresponding part of the spinal cord is intact causes a reflex of an undoubted inhibitory character; when the cord is destroyed the opening of the abdomen brings on a stimulation of peripheral inhibitory mechanisms and that, therefore, when the cord is intact the opening of the abdomen is instrumental in bringing out a two-fold inhibition—a reflex inhibition and an inhibition of a local peripheral mechanism.

These conclusions found their verification in results at which Cannon and Murphy[19] arrived in a series of different experiments. Cannon, as is well known, studies the movements of the gastrointestinal canal in

19. Cannon and Murphy: Jour. Am. Med. Assn., 1907, xlix, p. 840.

normal animals by the fluoroscopic method. In a series of experiments which he carried out together with F. T. Murphy it was found that crushing the testes of cats under anesthesia stops the peristaltic movements of the small intestines. When the splanchnic nerves were previously cut, however, the crushing of the testes did not interfere with the movements of the intestines. This shows that the crushing of the testes presents a stimulus which causes reflex inhibition of the intestinal peristalsis. Furthermore, Cannon and Murphy found that the transportation of food from the stomach through the intestines, which in cats does not stop by simple exposure of the intestines to the air, is greatly inhibited when the intestines are handled within the abdominal cavity and still more so when they are removed outside of the cavity and handled there. To test the nature of this inhibition Cannon and Murphy repeated these experiments in animals whose splanchnic nerves were previously cut. It was found that the handling still inhibits the movements. The inhibition called forth by the handling, therefore, is due to some local mechanism. Here again we have two varieties of inhibition —reflex inhibition and local inhibition of peripheral origin.

Before discussing the bearing of these facts upon the question of the nature of shock we shall first record some other observations brought to light by the investigations of Dr. Kast and myself in a series of experimental studies of the sensibility of the gastro-intestinal canal.

As is now well known, the observations made in human laparotomies under local anesthesia led the surgeons to the view that the abdominal viscera feel no pain and possess no sensory nerve fibers. In an extensive study which we made on dogs we found that the intestines are sensitive enough as long as they remain within the abdominal cavity and are very little or not at all exposed to the air. When the abdomen is freely opened and the intestines removed from the cavity the sensibility becomes greatly reduced or entirely abolished temporarily or even permanently. It is with sensibility the same as with motility; the sudden opening of the abdomen is like the sudden opening of a door which throws a hush on the lively company inside of the room. When the abdomen was opened under anesthesia and one loop of intestine was gently fixed between the branches of a dressing forceps and the abdomen then closed with temporary sutures, any moderate pressure on the protruding handle of the forceps invariably called forth an unmistakable sign of the sensation of pain. The result would remain constant for hours. If, however, all the temporary sutures were opened at once and stomach and intestines permitted to escape from the abdominal cavity,

in a minute or two the sensations of the intestines would be greatly reduced or completely abolished and would remain so for a shorter or longer period until the intestines were returned to the abdominal cavity and the abdomen closed or at least kept well covered with warm physiologic solution. We shall not enter here, of course, into any details of these experiments. We wish, however, to call attention to the following accompanying circumstances. Simultaneously with the loss of intestinal sensibility a distinct reduction of the sensitiveness of the skin over the entire body takes place, and at the same time the animal becomes distinctly apathetic. The dog, which a few minutes before was whining and restless, suddenly becomes perfectly quiet and strikingly indifferent, although the eyes are wide open and the lid reflex is active. A strong stimulus applied to the skin would wake up the animal, but only to sink again into the lethargic condition. The intestinal and skin insensibility and the general apathy set in even if the opening of the abdomen occurred in a warm bath of saline or Ringer's solution. The reduction of the sensibility of the skin is as a rule less pronounced than that of the intestines; the sensitiveness of the skin returns also a good deal sooner. The general apathy lasts a good deal longer. During all this time the blood pressure remains high; it may be as high as 150 millimeters of mercury or even higher. The pulse, which sometimes becomes rapid for a short time, soon returns to normal, and the respiration may be even slower than normally.

What does this loss of sensibility and apathy mean? With high pressure the phenomena can not be due to anemia, and with normal pulse, normal pressure and normal respiration it does not look like an exhaustion. Knowing now that the suppression of the motor phenomena by the opening of the abdomen is surely an inhibitory effect, we assume that the blunting of sensation and perception also means an inhibition, that is, an inhibition of the receptive sensory elements. Furthermore, since the processes of the reduction of the sensation from the skin and of the general apathy can take place only within the central organ, we have reason to assume that the stimulating factors combined with the opening of the abdomen create at the central end of the sensory nerves inhibitory processes which are responsible for the phenomena above described.

For reasons, into a discussion of which we do not wish to enter here, we consider it possible that in the nerve fibers of the intestines the peripheral receptive endings might also become somewhat affected by the opening of the abdomen. At any rate, the sensitiveness of the intes-

tines was distinctly more reduced than that of the trunks of the mesenteric nerves.

We may mention here an observation made by Dr. Auer and myself in studies upon the respiratory vagus. Although these studies are far from complete, the one fact which interests us here stands out quite clearly. It has been known for half a century that stimulation of the central end of a vagus nerve, especially in rabbits, affects the respiration so as to cause a standstill. Numerous investigations were made on this subject and there has been a contention among the various writers whether the standstill occurs in inspiration or in expiration. Standstill in inspiration means a tetanic contraction of the diaphragm, and standstill in expiration means an inhibition of the spontaneous contractions of the diaphragm. The inhibition occurs within the medulla oblongata and is of the same nature as the inhibition produced by the stimulation of the central end of the superior laryngeal nerve. Some years ago [20] showed that both statements are true, namely, that in some animals stimulation of the vagus causes standstill in inspiration, in others standstill in expiration. This means that the vagus contains two kinds of nerve fibers—stimulation of one kind causes excitation, that is, inspiration, and stimulation of the other causes inhibition of inspiration. Which of the effects prevails depends in each particular case upon conditions which are as yet unknown to us. We have now observed in a few dogs and rabbits that after the abdomen is widely opened stimulation of the central end of the vagus causes invariably an inhibition of inspiration. This means that the opening of the abdomen contains elements which favor the predominance within the medulla of an inhibitory state for the respiration. We may add that in these experiments, too, it was evident that the opening of the abdomen is the cause of a manifest reduction of the sensibility of the skin.

Turning again to our experiments on the sensibility of the abdominal organs, we have to point out a few more facts which are of special interest to our problem. In many of our dogs, especially in vigorous animals, blood pressure, pulse and respiration would remain normal for many hours, in fact the experiment had to be broken off before there was any sign of a so-called vascular shock. Meanwhile the viscera had been repeatedly eventrated and replaced in the abdominal cavity, the animal becoming more and more insensible to any stimulation and deeply apathetic while the blood pressure never was less than at least 100 millimeters mercury. In other animals the blood pressure dropped

20. Meltzer: Arch. f. Physiol., 1892, p. 340.

within two or three hours to 60 or 50 millimeters, the pulse ran up to about 180, the respiration was irregular and otherwise the animal presented the picture of deep shock. Again, in another comparatively small group of animals it came to pass that immediately after a sudden release of the temporary ligatures of the abdomen the animal sank into a state of deep shock. It lay absolutely motionless as if paralyzed; no manner of stimulation of the skin would bring out any reaction; the eyes were half closed with a completely indifferent look, though the lid reflex was not entirely abolished. The respiration was very slow and gasping, the pulse very rapid and small, although the blood pressure was still 70 or 60. The mucous membranes were usually pale, the viscera showing at least no hyperemia. The blood was always dark. All this would occur even when the opening of the abdomen took place in a bath of 40 degrees C. The animals of this group were far from vigorous, of a meek temperament and not well nourished. Even these animals did not die spontaneously; they were usually killed by clamping the trachea or by putting the tracheotomy tube under water, and the remarkable fact was then noted that in these animals the asphyxia did not result in any convulsions.

The shock seen in these few animals had a remarkable similarity to traumatic shock as described by Fischer and others in the human being, although in two of these animals the blood pressure was not lower than 60 millimeters.

From this series of experiments we have learned the following facts which have a bearing upon our problem. In all experiments in which our attention has been directed toward this point, opening of the abdomen and evisceration led invariably to a reduction of the sensibility of the skin and to general apathy, from both of which the animal is apt to recover sooner or later when the viscera are properly taken care of. While both of these conditions may attain sometimes a considerable degree of intensity, the heart and blood pressure may remain entirely unaffected. If the tough handling of the abdominal viscera continues, the insensibility and the general apathy increase. In vigorous animals this did not readily lead to a surrender of the functions of the body to complete shock, so that even after many hours of exposure and handling, blood pressure, heart and respiration still had suffered little. In less vigorous animals also the last named functions gradually surrendered to the effects of continuous rough handling of the viscera; these animals gradually sank into complete shock. Finally in animals with reduced bodily resistance complete shock appeared soon after laparotomy and evisceration.

In some cases an undoubted profound shock was present, although the blood pressure was not lower than 70 or 60 millimeters, a degree of pressure which, if not complicated by any other ill conditions, is still far away from the danger line.

We wish to point out especially that in our experiments in the cases in which the development of shock was gradual the symptoms of insensibility, general apathy and complete muscular relaxation invariably made their appearance long before the onset of cardiac and vascular breakdown.

Before continuing the discussion of our experiments further, I wish to make the following remark with reference to the symptoms of shock. In the above reported recent literature on shock low blood pressure is the paramount symptom, possibly also a rapid pulse. In the lucid description of traumatic shock of some of the older writers blood pressure was represented only by the few words that the arteries were of low tension, while there was a great deal to say about the peculiar mental state, the insensibility, the immobility, the respiration, etc. I may also mention here that in referring to Goltz's experiments on the effects of stroking the abdomen of frogs, usually only the condition of the heart and blood vessels is taken into consideration, while Goltz has expressly pointed out that as long as the animal is under the influence of the stroke reflex it is as if paralyzed and seems to be without sensation. Painting the leg with acid causes no reaction; later, when the animal recovers, it tries to get rid of the irritant. I emphasize these points to show that the symptoms of general apathy, of insensibility and of muscular weakness are integral symptoms of shock. The recent experimental studies on blood pressure in shock have, I believe, in some respects obscured the issue. Low blood pressure is surely one of the symptoms of shock, but it is not the only symptom. Again, it is not necessary in the definition of shock to assume the presence of blood pressure so low that the animals can not recover, as there is sufficient clinical evidence that recovery from shock may occur. Furthermore, there may be fatal shock without a very low blood pressure, and there may be very low blood pressure without the condition of shock.

While I do not wish to enter here into a detailed discussion of diagnosis, it seems to me quite safe to state that for the diagnosis of traumatic as well as surgical shock it is necessary to take into consideration the general mental state, the states of the sensibility and motility and the conditions of the cardiac, vascular and respiratory functions.

Returning again to our own experiments, we have seen that in animals of all degrees of vitality, laparotomy and handling of the intes-

tines leads to some degree of general apathy, insensibility and motor relaxation; in other words, to some of the symptoms of shock. This partial shock is not necessarily fatal and concerns functions which are not of immediate vital importance. With the prolongation of the exposure and handling of the viscera, the danger of the involvement of the cardiac, vascular and respiratory functions increases, and the danger is the greater the lower the vital resistance of the animal. The last-named functions are of greater importance for the continuation of life and are, therefore, in the vigorous animal provided with greater factors of safety, so that minor assaults do not easily shake their foundation.

Generalizing our experience, we may say that the sudden opening of any body cavity will frequently cause a partial shock which may consist of the anesthetic condition of the contents of this cavity, a reduction of general sensibility and a general muscular relaxation. When the handling of the contents of the cavity is continued and the powers of resistance of the subject are at a low point, a more or less complete shock develops, in which other more vital functions become involved in varying degree; sometimes the heart, sometimes the vascular system, and sometimes the respiratory mechanism, are predominantly affected. Similar conditions may be brought on by extensive dissections or burning of some parts of the body; it should be borne in mind that one part may perhaps react more readily than another. Beside these intentionally produced or accidental injuries, violent mechanical agitation of some especially sensitive part without actual destruction of tissue might also be capable of calling forth more or less complete forms of shock. All these various methods of producing partial or complete shock represent in one form or another strong stimulations abruptly applied to the normally tranquil nervous system.

What is the nature of that condition which we term shock? We are in the habit of expecting a stimulus to produce or increase an activity. In shock the activity of the functions is depressed or suspended. By what method do the stimulating injuries cause this depression or suspension of activity? The current view is that the depression is a state of exhaustion or fatigue of the functions or of the nerve cells controlling them. In estimating the value of this hypothesis, one should remember that it was first advanced to account for the inhibitory effect of the vagus upon the heart. The objectors to the new idea of inhibition tried to explain the fact of the arrest of the heart's action by assuming that the vagus was the motor nerve of the heart, and that the cutting of the nerve caused fatigue of the heart by overstimulation.

Since this time this has been the favorite hypothesis of some writers to explain any reduction of activity of the nervous system. The fact that no hyperactivity of the function precedes its depression does not seem to have any weight with these writers.

In our own experiments upon the motility of the gastrointestinal canal we have seen that the dissection of the skin produced a suspension of the normal movements which could not depend on fatigue and exhaustion, since the destruction of the cord restored the function of the gut to even greater activity. It was evident that in this case the dissection of the skin gave rise to an inhibition of the motor function of the gastrointestinal canal similar in character to that of the cardiac inhibition. Furthermore, in the studies of the effects of the stimulation of the vagus on respiration, it was found that opening of the abdomen favored the inhibitory response to stimulation to the central end of that nerve. These facts demonstrate that dissections of the skin or opening of the abdominal cavity do not produce exhaustion, but result in a more active inhibition.

On the other hand, Howell has called attention to the fact that the vascular depression in shock is not preceded by increased activity sufficient to justify the assumption of exhaustion from over-stimulation of the center. Furthermore, in the stroke experiments of Goltz, the general paralysis and the anesthesia prevalent during the stroking of the abdomen is never preceded by tetanus or hyperesthesia.

On the basis of these considerations I venture the assumption, which is not new, that the various injuries which are capable of bringing on shock, do so by favoring the development of the inhibitory side of all the functions of the body. This predominance of inhibition makes its appearance at first in those functions which are of less immediate importance to life, and are, therefore, less insured by safeguards protecting their equilibrium. With increased injury the inhibition spreads also to the more vital and, therefore, better protected functions of the nervous system. The early inhibition in the development of shock, of the functions of lesser importance, might even be looked on as being, in a degree, conservative measures of protection of other more important functions of animal life. The restfulness of the body, the painlessness and mental indifference are certainly most desirable conditions in the management of shock of the more vital functions.

We shall say here a few words as to the meaning and importance of inhibition in connection with our problem. The body's functions are clearly constructed on the dual principle. The heart has the accelerators as motor, and the vagi as inhibitory nerves. The vascular system has

in the centrifugal direction vasoconstrictors and vasodilators, the latter having simply inhibitory functions. In the centripetal direction there are nerve fibers which increase the tonus of the vasomotor center, as the fibers within the sciatic nerve, and there are nerve fibers which inhibit and depress the tonus, as the depressor nerve. For the respiratory centers there are fibers which augment inspiration, as certain fibers in the vagus, and others, as the superior laryngeal nerve, which inhibit inspiration. The same holds good for expiration. For the gastrointestinal canal the vagus is essentially a motor nerve and the splanchnic nerve essentially an inhibitor. These instances will suffice to support the contention that the functions are not kept up simply by acting when there is a stimulus to them and by resting when a stimulus is lacking. They are, on the contrary, constructed on the dual principle, on a well-balanced antagonism between excitation and inhibition. During life there is never an absence of stimuli; they stream continually in legions from outside and are ever present in the blood and lymph. The normal state of a function results from a proper balance of antagonistic stimulations, and the important functions are well provided with factors of safety to keep up the normal equilibrium.

Under unusual abnormal conditions, however, there may arise a tendency toward a deviation in one or the other direction; that is, in the direction of excitation or in that of inhibition. With regard to shock, our theory assumes that the injuries which produce shock disturb the equilibrium, causing a tendency toward inhibition. It certainly does not mean reducing the function to a single principle, to inhibition alone; it only means shifting the tendency toward inhibition. Stimulation of nerve fibers which usually cause excitation will still cite, and fibers which cause inhibition will still inhibit and probably inhibit even better than in a normal state. Porter's experiments showing that in shock the depressor is very active, more so even, than when the blood pressure is normal, is far from being evidence against the theory that in shock the vasomotor center is more favorable toward inhibition; on the contrary, it would tend to support this idea.

The assumption that the insufficient activity of several functions during shock is due to a preponderating inhibitory influence refers only to the primary effect. It seems to me self-evident that during the course of shock other influences must become secondarily active. The insufficient activity of one function becomes detrimental to the other, and anemia, asphyxia or even fatigue or other conditions might become operative during the progress of shock.

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CHLOROFORM NECROSIS OF THE LIVER.*

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The occurrence of serious, frequently fatal, poisoning as a sequel of chloroform anesthesia, manifesting itself first several hours or even a few days after the use of the drug, has been brought into prominence through the articles of Ballin, Bevan and Favill, Brewer, Brackett and others in this country, and of Guthrie in England; therefore, it is unnecessary for me to discuss the literature at length, as this will be found fully abstracted to 1905 in the article of Bevan and Favill,[1] and subsequent articles are indexed in the foot notes to this article.

REPORT OF THE CASE.

I desire merely to report a study of both the pathologic anatomy and the chemistry of a typical case, which I had the opportunity of examining at autopsy, through the courtesy of Dr. F. S. Tufts, and to consider certain features illustrated by this case and those so far recorded in the literature. Dr. Tufts has kindly furnished me the clinical history, which follows:

Clinical History.—"The patient, a vigorous young man, was born in Wisconsin in 1878. The family history is negative. He came to Chicago in 1899, and has been employed as a foreman in the hog-casing department of a packing house. In 1900 he married a first cousin, who gave birth to a healthy boy in 1904. His childhood history was negative, and up to 1902 he was strong, robust, and of very good color. In 1902 he lost weight and color, and began to complain of an occasional stomach trouble. He had no acute attacks or colic, but occasionally there was acute distress from gas after meals, with a sensation of fullness. The first acute attack of colic and cramps occurred on Jan. 1, 1907, and was brought on by a hearty packing-house restaurant dinner. I saw him two hours after the attack and found slight tenderness in the umbilical region, but nothing around or near the gall bladder; he returned to work the next day and was free from trouble until March 17. This second attack was apparently caused by fruit salad which he had eaten the day before. At this time I found no fever, some rigidity in the right rectus, but not much tenderness; he had had colic and cramps all night but not severe enough to call me. On the next day, March 18, he went to work, although still a little lame, and the following day visited me at my office, when the gall bladder was found markedly distended; it extended 10 cm. below the costal arch, was freely movable and slightly tender. At this time there was no fever, no icterus, nor even bile in the urine (Gmelin's test). On the next day his condition was about the same, although the temperature was 99.2, pulse 78. The following day (March 21) the temperature was normal and the tenderness was

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1. Bevan and Favill, Jour. Am. Med. Ass'n., 1905, xiv, 691-696.

subsiding, but he was quite pale and complained of feeling very weak; in the evening he was taken to the Englewood Hospital." Here his pulse, temperature and respiration were recorded as normal, and he was prepared for operation, which was performed at 4 p. m. on March 22.

Anesthesia.—The anesthetic was chloroform and it was "given with a free hand" by the anesthetizer, and cyanosis was very marked. The duration of anesthesia, however, was not long, as it is recorded that the patient left the ward for the operating room at 4 p. m., returned at 5 p. m., and was again conscious at 5:30 p. m.

Operation.—When the abdomen was opened the upper surface of the liver was found freshly adherent to the parietal peritoneum, while the lower surface, gall bladder and intestines were bathed with lymph and fresh adhesions everywhere. The gall bladder was thickened, but neither it nor the ducts were distended, and no stones could be palpated. On account of the evidently acute nature of the infection it was deemed wiser not to open the gall bladder, and the bad way in which the patient was taking the anesthetic impelled haste, so the abdomen was closed again without draining the gall bladder.

Postoperative History.—Following the operation the patient slept fairly well and the next day at noon the temperature rose to 99.7, but subsided on the following morning, March 24, although at this time there was a leucocytosis of 17,000. All this day the patient was in good condition, sleeping much of the time, until 11 p. m., fifty-five hours after the operation, when he began to be restless. By 3 a. m., March 25, he began to be delirious, acutely maniacal, and was unconscious from that time on, although he could be roused somewhat by calling. On the morning of this day the temperature at 10:30 was 99.3, pulse 82, respiration 22. The patient was very thirsty, icterus began to appear, and the urine, which before the operation had been normal, now showed much bile, albumin and hyalin and granular casts, but no crystals of leucin or tyrosin could be found. Under the influence of chloral and bromids the patient became more quiet at about 4 p. m., laughter and crying taking the place of the wild delirium previously exhibited. The jaundice had increased during the day. By 3 p. m. the temperature had risen to 103; at 5 p. m. it was 104; at 7 p. m., 106; and at 8 p. m., 107. Death occurred at 9:30 p. m., 100 hours after the operation.

Autopsy.—This was performed at 9 o'clock the next morning, in the undertaker's room, to which the body had been removed. An attempt at embalming with an arsenical solution had been made just before our arrival, but fortunately this was so ineffectually done that practically none of the fluid penetrated the viscera and tney were almost unaffected; however, there had been some fluid introduced directly into the peritoneal cavity, which interfered with cultures being made from the peritoneal exudate and gall bladder; while of course blood cultures were made valueless by the intravascular injection.

Autopsy Report.—This is summarized below.

Anatomic Diagnosis: Acute hepatic degeneration and atrophy. Cholelithiasis with chronic suppurative and proliferative cholecystitis. Acute fibrinous pericholecystitis. Suppurative cholangitis with fibrous pericholangitis. Partial occlusion of cystic duct near juncture with hepatic duct. Recent operative incision in right hypochondrium. General icterus. Multiple ecchymoses in serosa of thoracic and abdominal cavities. Hypostatic pulmonary congestion. Right inguinal hernia.

External Appearance: Young man, slenderly built; fairly nourished; very icteric all over the body, especially the face; sclera bright yellow. Scar of old trauma over right tibia. Recent operative incision three inches long in right hypochondrium; also embalmer's incision in right arm. Discolored skin areas from saline transfusion over both pectorals. Right inguinal canal open a short ditsance.

Abdominal Cavity: Distended by clear embalming fluid (arsenic and bichlorid of mercury). (Clinically it was flaccid up to death.) Omentum free. Numerous small blood extravasations throughout omentum. Many hemorrhagic foci, size of pea and smaller, scattered throughout mesentery and retroperitoneal tissue. Several larger suggillations more sparsely distributed. Appendix free; three inches long, no mesoappendix; no changes.

Gall Bladder: Adherent to colon and pylorus by fresh, easily torn, fibrinous adhesions. Surface of gall bladder covered by fibrin, beneath which are numerous hemorrhagic extravasations into the subperitoneal tissues. Gall bladder wall greatly thickened, about 5 to 8 mm. thick. On palpation the bladder apparently semi-solid; cystic duct thickened and distended. Lesser peritoneal cavity free. Diaphragm at fourth rib on both sides. Slight adhesions about spleen.

Chest: The entire mediastinal tissue riddled by ecchymoses, averaging about the size of a pinhead. Pericardium studded with the same. Pericardial cavity normal. Both pleural sacs free from adhesions. Pleura everywhere studded with small ecchymoses.

Heart and Great Vessels: Normal. Portal system free from thrombi.

Lungs: Posterior parts of each lung congested and darker than the anterior and contain much fluid. (Probably part is embalmer's fluid; no clinical indication of edema before death.)

Liver: This is small; weight 1,050 g. The margin is two fingers' breadth above costal margin. The right lobe has been superficially hardened by embalming fluid. The left lobe is not hardened to any extent. The latter is very flabby, pinkish gray in color and looks almost as if decomposed. The anterior margin is very sharp. Surface discolored to a dirty pinkish-gray color and somewhat wrinkled. The right lobe shows the lobular marks with unusual distinctness on the external surface, as a fine network of lighter gray lines with reddish hexagonal areas between. The cut surface of the right lobe shows the same mottling as seen externally, and is of a light yellow tinge. The left lobe is very distinctly yellow; the lobular markings are difficult to distinguish. The consistence is very flabby so that the liver can be folded upon itself. The bile ducts and large vessels show no evident changes. On pressure on ductus choledochus, a purulent yellow fluid exudes into the duodenum from the ampulla of Vater. On incision of gall bladder a yellow muco-pus escapes. In the bladder are over 100 stones, black, hard, varying in size from 3 mm. in diameter down to that of the finest sand. The gall bladder wall is 6 mm. thick. There is nearly total obstruction of cystic duct near its junction with the hepatic duct by a fibrous occlusion (scar tissue) and pressure of a mass of recent fibrous tissue about the duct. The hepatic duct seems to be normal. A few stones occur in the ductus choledochus. The latter shows an inflammation and swelling of the mucosa.

Spleen: Apparently normal. Very much hardened by embalming fluid.

Pancreas: No evidence of fat necrosis, and no other change observed.

Kidneys: Somewhat hardened by embalming fluid. Normal size. Capsule strips normally; no evident pathologic alterations.

Adrenals: Normal.

Histologic Findings.—Liver: There is not a normal liver cell to be found, and very few, indeed, that are not totally necrotic. At first glance the liver resembles an organ that has undergone extensive postmortem decomposition, but it is soon seen that only the parenchyma cells have beeen affected, and that there are quantitative differences between the conditions in the center and periphery of the lobules. The lobules are somewhat reduced in size and only at the very periphery of the lobules can there be found parenchyma cells that show any approach

to the normal structure; these cells are never more than one or two layers deep from the periportal tissue, and the best of them show cloudy swelling and fine granules of fat. Immediately next to these cells is a narrow zone, representing a width equal to two to ten liver cells, in which the cells consist of a mere meshwork of fat droplets with no cytoplasm remaining and only exceptionally a nucleus. In all the rest of the lobule, which part constitutes from two-thirds to four-fifths of the entire radius of each lobule, is total necrosis of the liver cells; nothing remains of them but the dead bodies of the cells, deeply stained by eosin and evidently greatly reduced both in size and number. There is no thrombosis in the hepatic capillaries, no acute or chronic inflammation, and no evidence of alteration in the bile ducts. By sudan III the necrotic central cells are found rarely to contain small fat droplets, although between them can be found Kupfer cells that are quite fatty. The vacuolated zone near the periphery is composed of cells containing large amounts of fat, and the most normal peripheral cells show numerous fat droplets.

Kidney: Epithelium of convoluted tubules is granular and many of the tubules are swollen shut, and some contain occasional fat droplets; these are especially numerous in the straight collecting tubules. Some of the epithelial cells seem to be necrotic. The glomeruli contain a considerable amount of granular debris, but otherwise no changes. There is no hemorrhage, acute inflammation or connective tissue increase.

Spleen, Myocardium and Pancreas: No changes found, except a small amount of fat in some of the muscle cells of the heart.

Gall Bladder: Diffuse infiltration of the wall with lymphoid cells, plasma cells and some polymorphonuclear leucocytes.

Chemical Examination of Liver.—Immediately after the autopsy the liver was cut into thin slices, and 850 grams of the fresh tissue were placed in a large volume of 95 per cent. alcohol until thoroughly hardened, and then subjected to chemical analysis, the details of which will be published elsewhere.[2] The chief results of this study may be summarized as follows: Among the water-soluble substances obtained by extraction of the liver tissue were considerable quantities of free aminoacids, presumably derived from the proteins of the liver cells through autodigestion; of these aminoacids there were obtained in pure enough condition for identification 0.34 gram of histidin, 0.26 gram of tyrosin; 1.50 grams of leucin, 1.57 grams of glycocoll and 0.58 grams of glutamic acid. The presence of arginin, lysin, and pyrrolidin-carbonic acid could not be definitely established, although there was obtained evidence which indicated that these substances were in the extracts. A further indication of the autolytic destruction of the liver proteins that was going on in this case was the finding of considerable quantities of proteoses, peptones, and probably of polypeptids. Free xanthin and hypoxanthin were also found in the extracts, undoubtedly derived through autolytic disintegration of the nucleoproteins of the liver cells. There was no increase in the gelatigenous substance of the liver, such as has been observed in acute yellow atrophy, since this is the result of regenerative proliferation of connective tissue, which had not begun to take place in the chloroform necrosis liver. The composition of the insoluble coagulated proteins left after thorough extraction of the liver with alcohol, ether, and cold and hot water, was found to be quite the same in this liver as in two normal livers, at least so far as the form in which the nitrogen is bound; whereas a liver from a typical case of advanced acute yellow atrophy showed some loss of diamino-nitrogen. This is shown in the following table giving the results of analyses of these four cases by Hausmann's method:

2. Wells, H. G.: Jour. Biol. Chem., 1908, vol. v.

COMPARISON BETWEEN ACUTE ATROPHY, NORMAL AND CHLOROFORM NECROSIS LIVERS.

	Acute Atrophy.	Normal (anemic)	Normal (congested)	Chloroform Necrosis.
Amid nitrogen	5.5	3.7	4.8	3.9
Humus nitrogen	3.6	3.4	4.9	5.7
Diamino nitrogen	26.2	32.8	30.0	30.0
Monamino nitrogen	64.8	60.3	60.2	60.3

This same insoluble residue, which consisted chiefly of proteins, contained the same amount of sulphur as normal liver extracted under the same conditions. The amount of iron was slightly increased, presumably because the hemolysis that always occurs in jaundice sets free iron-containing pigment which the liver stores up. Phosphorus was found increased by three or four times the amount found in normal livers, and this in spite of the great destruction of nuclei that had taken place. No satisfactory explanation for this increased amount of phosphorus has been found.

There was found 72.4 per cent. of water in this liver, 8 per cent. of fats and lipoids and 18.8 per cent. of dry, fat-free solids, which is somewhat different from the proportions found in typical acute yellow atrophy, as shown by the following table:

	Water.	Fat.	Fat-free Dried Substane.
Normal liver (Quincke)	76.1	3.0	20.9
Normal liver (Wells)	77.6	5.0	17.4
Acute atrophy (Perls)	81.6	8.7	9.7
Acute atrophy (Perls)	76.9	7.6	15.5
Acute atrophy (v. Starck)	80.5	4.2	15.5
Acute atrophy (Taylor)	85.8	2.0	12.2
Acute atrophy (Wakeman)	79.3	...	...
Acute atrophy (Wells)	83.8	2.5	13.7
Acute atrophy (Voegtlin)	78.0	6.6	15.4
Phosphorus poisoning (v. Starck)	60.0	29.8	10.0
Fatty degeneration (v. Starck)	64.0	25.0	11.0
Chloroform necrosis (Wells)	72.4	8.8	18.8

In respect to the amount of water, this chloroform necrosis liver stands between the typical acute yellow atrophy liver and the ordinary fatty liver, just as it does in its histology; that is, there has been some replacement of water by fat, as in the fatty livers, but not so much replacement of protein by water as in typical acute yellow atrophy. These figures emphasize the fact that in chloroform necrosis the amount of fat is distinctly increased, although not so much is found on analysis as might be expected from the microscopic findings. Taylor states that, in the chloroform necrosis liver which he examined, there were 200 grams of fat, which would be about twice the proportion that was found in my case; unfortunately he has not published sufficient details of the analysis to furnish the accurate information desired.

The amount of lecithin and cholesterin in this case was found to be not greatly different from that present in normal livers, and thus again in marked contrast to the liver in acute yellow atrophy, as seen by the accompanying table.

While the total amount of lecithin has decreased, this is only in proportion to the decrease in the total size and weight of the liver; this proportional decrease has gone on in spite of a relative increase in the amount of simple fat, showing the same lack of correlation between the lecithin and the neutral fat which has been observed by others who have determined the lecithin content of organs showing fatty degeneration. Evidently, therefore, the increase in the fat content of the liver in chloroform necrosis is due entirely to neutral fats. The cholesterin, on

the other hand, has apparently remained in about the normal amount, and has not decreased with the lecithin and proteins; this is quite what might be expected from what we know of the tendency of cholesterin, when liberated by degenerating cells, to remain at the place where it is formed.

	Lecithin.				Cholesterin.			
	Normal. (Anemic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.	Normal. (Anemic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.
Fresh weight, per cent.....	1.6	1.4	1.5	0.45	0.26	0.37	0.52	0.3
Total dry weight, per cent.....	6.3	6.25	6.2	2.9	1.0	1.7	1.9	1.8
Dry, fat-free material, per cent.	7.7	8.0	8.1	3.2	1.25	2.1	2.9	2.1
Ether-soluble substances, per cent	35.3	28.0	17.3	17.6	5.7	7.4	5.9	11.1
Grams in entire liver.....	23.7	22.4	16.0	4.4	3.8	5.95	5.4	3.38

GENERAL CONSIDERATIONS.

If we examine carefully the cases of "delayed chloroform poisoning," as reported in the literature under various titles, it becomes apparent that there are included two fairly distinct types of cases resulting from the same cause, and that these types differ both clinically and anatomically. In one set the patient is usually a child; the clinical manifestations are vomiting, restlessness or extreme excitement, terminating in coma, frequently more or less cyanosis, and sometimes definite air hunger, a sweetish odor of the breath and acetone bodies present in the urine in most of the cases in which they were sought for; in other words, the symptoms resemble in many respects "acidemia" or "acetonemia," under which titles many of these cases have been described. The liver in these cases generally shows more or less fatty change; usually when described carefully the fat is said to have been chiefly in the periphery of the lobules, and there is no mention of necrosis of the hepatic cells in the published accounts of these cases. Generally, fatty degeneration and more or less acute parenchymatous degeneration, sometimes even severe necrosis, are found to have taken place in the kidney. In practically none of these cases has jaundice been observed, and the liver changes have not usually been very severe. To this group belong all but perhaps one or two of the cases described by Guthrie, and the cases of Brackett, Brewer, and Telford and Falconer.

Quite different from this group are the cases of Stocker, Bandler, Erlach, Marthen, Mintz, Ballin, Campbell-Horsfall, Guleke, Cushing, Taylor, Holmes and the one described in this report. Here the clinical picture at first is rather similar to the first group, in that the onset is usually with restlessness, excitation, and delirium, which passes into coma. However, in place of those symptoms which are usually considered as manifestations of acetonemia, there appears a rapidly developing

jaundice, which toward the end is generally very severe. Associated with this jaundice are frequently observed cutaneous hemorrhages. The manifestations resemble in every respect a severe cholemia, associated in some cases with the finding of leucin and tyrosin crystals in the urine. Consequently several of these cases have been reported under the title of "acute yellow atrophy of the liver," which diagnosis is supported in the main by the anatomic findings at autopsy. The liver is usually decreased greatly in size, with wrinkled capsule, friable consistence, and yellowish or red and yellow discoloration; often the organ is so severely disorganized, as in the cases of Taylor and the one here reported, that it may be best described as "putty-like." While there is always more or less fatty increase, this is usually more apparent than real, much of the yellow color commonly described as "fatty degeneration" being due to bile pigments; necrosis is the predominant change, beginning in the center of the lobules, as in typical "idiopathic" acute yellow atrophy.

I have had the opportunity to study the histologic appearance of three typical cases of this kind, including one that was reported by Dr. Bayard Holmes[3] and, through the kindness of Dr. Hektoen, the case reported by Drs. Bevan and Favill, and the resemblance of the findings in all three is very striking. As compared with the histologic picture described above in connection with the case which is the subject of this report, the differences are but slight. The Holmes case differs only in having a slightly wider zone of well-preserved cells in the periphery and in the presence of more leucocytes, especially at the junction of the fatty and the necrotic zones. In the case of Bevan and Favill, which clinically was without jaundice or other evidence of hepatic involvement, the fatty zone is very much wider, and the necrotic central cells contain more numerous and larger fat droplets; the size of each lobule is, if anything, increased rather than shrunken. But, taken all together, the histologic picture is strikingly similar in all three livers, practically identical in fact, and indicates the specificity of the effects of chloroform on the liver.

This necrosis is associated with rapid autolysis of the dead cells, so that in my case the weight of the liver had fallen in four days to 1,050 grams, presumably from a normal weight of from 1,600 to 1,800 grams. As a result of this autolysis, leucin and tyrosin may appear in the urine, and free amino-acids may be found in extracts from the liver itself. Of particular interest is the fact that in all the reported cases of this type, as far as I can find, the patients were adults, varying from 20 to 42 years of age; whereas, in the acetonemia type, the patients were nearly all young children. The Bevan and Favill case, in "a girl, aged 12½ years,

3. Holmes, Bayard: Appendicitis, 1904, p. 214.

with the stature of a woman," seems to lie at the border line between the two groups, for clinically there was no jaundice and the manifestations were of the "acetonemia" type, but histologically the liver, which was enlarged rather than shrunken, showed a considerable amount of central necrosis, although the fatty changes were more marked than in either of the other two cases that I have studied, and the necrosis and autolysis a little less extensive.

Both sexes are represented in each type, with perhaps a slight preponderance of females. Why there should be this difference in the results of delayed chloroform poisoning in children and in adults I do not know, but the number of cases reported is too large to make it seem purely a matter of coincidence. Nearly all reported cases of fatal delayed chloroform poisoning seem to have occurred in the young, only two or three patients having reached the forties. Consequently there appears to be some difference in the liver or in the entire organism between youth and later life that determines this susceptibility to chloroform. In young adults the susceptibility of the liver seems to be particularly great, so that severe necrosis of this organ, with symptoms of hepatic insufficiency, dominates the anatomic and clinical picture.

The changes in the liver, in this second type of delayed chloroform poisoning, are not essentially different from the changes in the early stages of acute yellow atrophy, except that there seems to be a more extensive fatty degeneration and infiltration. In true acute yellow atrophy there is no distinct increase in the proportion of fatty matter in the liver, while the total amount of fat is decreased more or less from the normal, along with the general loss of hepatic substance. In chloroform necrosis there is always more or less fatty metamorphosis noticed microscopically, and in the two cases in which the fat was extracted and weighed, Taylor's and my own, the amount of fat was distinctly increased above normal. It is possible that if one were to secure a liver in chloroform necrosis as long after the onset of the hepatic injury as is the case with acute yellow atrophy, where death occurs usually only after weeks rather than days, the changes might be found still more similar, for I have found that it is possible for a fatty liver to lose much of its fat and to have the fat replaced by fluid during the healing stages of the hepatic lesions produced by hydrazine poisoning.[4] However, even with this disparity of time, the results of analysis of a liver in idiopathic acute yellow atrophy of several weeks' duration are, on the whole, very similar to those obtained with this chloroform necrosis liver,[5] and

4. Wells, H. G.: Pathologic Anatomy of Hydrazine Poisoning. Jour. Exper. Med., 1908, x, No. 4.

5. Wells, H. G.: Chemistry of the Liver in Acute Yellow Atrophy, Jour. Exper. Med., 1907, ix, 627.

I can not take issue with those who have diagnosed their cases of delayed chloroform necrosis as acute yellow atrophy. Nevertheless, I believe that it would be well to reserve this term for those cases of hepatic atrophy which occur without evident cause, and which are characterized by a widespread necrosis of the liver cells without fatty metamorphosis, followed by rapid autolysis and removal of the necrotic cells, and early proliferative activity of the interstitial tissues and the bile duct epithelium. As a particular characteristic of this disease should be mentioned the fact that the organs other than the liver seem scarcely to suffer at all or only secondarily to the hepatic insufficiency. Chloroform necrosis, puerperal eclampsia, and certain violent septicemias, produce changes in the liver that are more or less similar to those described above, but never quite the same, especially in the relatively great injury of other organs and the extent of fatty changes in the liver; therefore, I believe that we would do best to refer to these several forms of hepatic necrosis by the names of the condition causing them, considering the typical "idiopathic acute yellow atrophy" as a pathologic entity, which perhaps may be found to have a specific cause.

As to the reason for the severe effects that chloroform sometimes produces on the liver, some time ago I advanced a hypothesis somewhat as follows:[6]

> Chloroform is a protoplasmic poison for cells of all kinds, stopping their synthetic activities but not seriously impairing their autolytic enzymes. This we see if we add chloroform to a culture or emulsion of bacteria, the cells at once die and begin to undergo autolysis. In view of the nature of the changes that occur in the liver in chloroform necrosis it seems probable that a similar effect has been produced by the chloroform upon the liver cells, that is, their synthetic activities are checked, and autolysis goes on unbalanced by constructive processes. Presumably it is the oxidative enzymes that are chiefly affected by chloroform, for, if these were destroyed, the resulting changes would be exactly what we observe taking place in chloroform necrosis; that is, the lipase would act unbalanced by the normal oxidative destruction of fatty acid and glycerin and so fat would accumulate in the cell, while at the same time synthetic changes, which seem to depend upon oxidative processes and the correlated reductions, would be stopped, and autolysis would assume the upper hand. While at the present time we have no means of determining the correctness of this hypothesis, still it can be said that nothing that is not in harmony with this theorization has yet been learned concerning the processes that take place in chloroform necrosis. Chemical analysis has merely corroborated the anatomic evidence of autoloysis and fat increase in the liver cells.

Just why the liver should only occasionally suffer this serious injury from chloroform is still unexplained. Although in my own case it is probable that excessively free administration of chloroform may have been of influence, in many of the recorded cases this explanation has not been available, for often it is stated specifically that only a small amount

6. Wells, H. G.: Delayed Chloroform Poisoning and Allied Conditions, Jour. Am. Med. Ass'n., Feb. 3, 1906, xlvi, 341.

of chloroform has been used. There is abundant evidence that anything that impairs oxidation favors the occurrence of chloroform poisoning, and diseases that are prone to affect the liver, especially those that of themselves frequently cause fatty changes in the liver, are said, by all who have studied delayed chloroform poisoning, to be important predisposing factors. As a possible explanation of this apparent relation of pre-existing fatty changes in the liver to chloroform necrosis of the same organ, I would make the following suggestion:

Chloroform, like other anesthetics, seems to owe its effect on the nervous system to the fact that it is a strong fat solvent, and hence is taken up by the lipoids of the nervous tissues. This fact was first brought out by Overton and Meyer. The amount of chloroform that a tissue will take up, therefore, depends on the amount of fatty material in it which can dissolve the chloroform out of the blood; this is on the same principle as the method used in the laboratory for separating substances of different solubility in water and ether, water and chloroform, or other immiscible liquids, for the substance in solution distributes itself between the two solvents according to its solubility in each. This phenomenon is manifested when anesthetics are administered to obese persons, whose fatty tissue absorbs so much of the anesthetic that it requires a correspondingly larger amount to affect the nervous system. It would seem probable, therefore, that a fatty liver would abstract much more chloroform from the blood than a normal liver, and that this chloroform would thus act more strongly and for a longer time on the protoplasm of the fatty liver cells than it would in a normal liver.

As to the fact that the necrosis observed in these livers is in the center of the lobules, and that the fatty changes are sometimes central and sometimes peripheral, it would be hazardous to offer an explanation. This distribution of the hepatic lesions in the lobule is always a puzzling question, for, although we can construct explanations on the basis of the fact that poisons first reach the lobule at its periphery and that the oxygen supply is poorest at the center, yet we always find that exceptions are so abundant for any rule we may attempt to formulate that our attempted explanations of the observed facts have no value. For example, in phosphorus poisoning in most of the lower animals we find the fatty changes beginning at the periphery of the lobule; yet in monkeys and apes the changes are said to be central; furthermore, another steatogenetic poison, hydrazine, always produces the fatty changes in the center of the lobule in the same animals in which phosphorus attacks the periphery.

The necrosis of the liver in puerperal eclampsia is ordinarily periph-

eral, and is ascribed to capillary thrombosis. Mulzer[7] found that chloroform administered to rabbits rapidly produces fibrinous thrombi in the capillaries, especially of the lungs, but also in the liver and kidneys. These thrombi are probably initiated by the clumping of injured red corpuscles, and their development is favored by the increased coagulability of the blood, which develops during the anesthesia. It is well known that injection of substances that cause agglutination of the red corpuscles produces extensive necrosis of the liver tissue, but the distribution and appearance of the lesions produced by agglutination thrombi are quite dissimilar to the lesions of chloroform necrosis. In my own specimens, from two cases, I was unable to demonstrate capillary thrombi by Weigert's fibrin stain, and in other cases in the literature the report of the pathologic anatomy is far too incomplete to permit one to judge as to the presence or absence of such thrombi. Of course, it might be possible to explain the anatomic and clinical findings on the basis of capillary thrombosis, if this existed to a sufficient extent, but so far there is no evidence of the occurrence of such a process. It has been suggested that chloroform lowers the normal power of the blood to inhibit autolysis, and if this were extensive enough it might account for the sudden autolysis of the liver that appears in chloroform poisoning. Studies of the inhibiting power of the serum of animals during chloroform anesthesia might throw some light on this.

Two therapeutic hints that have recently appeared seem to be well enough supported by the pathologic and clinical observations to be referred to in closing. J. H. Lyons, of Seattle, in discussing the treatment of puerperal eclampsia,[8] objects to the prevalent custom of suppressing the convulsions by the use of chloroform, often for long periods of time. The similarity of the effects of chloroform and puerperal eclampsia on the liver, and the well-established fact that pre-existing injury to the liver predisposes to delayed chloroform necrosis, are certainly weighty reasons for this caution. It is also quite probable that chloral is not altogether a safe sedative in cases of this kind, since it is known to produce changes in the liver similar to those caused by chloroform. Beddard[9] suggests that in the treatment of chloroform necrosis, and more especially for its prevention in cases where it is deemed necessary to use chloroform in spite of possible existing disease of the liver,

7. Mulzer: Die Auftreten intravitaler Gerrinungen und Thrombosen in der Gefässen innerer Organe nach Aether-und Chloroformnarkosen. München med. Wchnschr., 1907, liv, 408.

8. Lyons, J. H.: Northwest Med., December, 1906.

9. Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet, March 14, 1908, p. 782.

the administration of glucose may be of value. This suggestion is based on Rosenfeld's view that poisoned hepatic cells can utilize carbohydrates well, but proteins and fats only poorly, and that consequently when the cells have used up their meager store of carbohydrate they are unable to utilize the proteins and fats that are available, and hence undergo starvation and death. Experiments have shown that feeding of dextrose to animals lessens the amount of fatty degeneration which results from phosphorus poisoning, and presumably it should have some similar effect in chloroform poisoning.

SUMMARY.

The cases of delayed chloroform poisoning described in the literature apparently tend to group themselves into two classes. In one, which affects chiefly children, the symptoms are those of "acidemia" or "acetonemia," without jaundice, and in these cases the changes of the liver are not so very marked, consisting, according to the published descriptions, chiefly of fatty degenerations about the periphery of the liver lobules. The other type is observed chiefly in young adults, and clinically is marked by profound jaundice, cholemia, hemorrhages, and the usual symptom-complex of a rapidly fatal acute yellow atrophy of the liver; anatomically the liver appears much as it does in acute yellow atrophy, being reduced in size, flabby, yellow and showing microscopically an extreme degree of necrosis, beginning in the center of the lobule, with more or less peripheral fatty degeneration. Intermediate cases occur that do not fall distinctly into one or the other of the two types. Histologic study of these cases of the second type, to which the name "chloroform necrosis of the liver" may be appropriately applied, shows a striking constancy of structural changes; these consist of total necrosis of all the liver cells, except those at the periphery of the lobule, with autolytic disintegration of the necrotic cells, and fatty degeneration of those cells that are not necrotic. The capillaries and bile vessels do not seem to be affected; there is no thrombosis and no inflammation or proliferative reaction. Chemical analysis corroborates the histologic evidence of fatty changes and autolysis, there being found a slightly increased amount of fat, and the presence of considerable quantities of free amino-acids, purins, proteoses, peptones and polypeptids, derived from the autolysis of the cells.

The condition in the second set of cases resembles very closely that of typical acute yellow atrophy of the liver, except in the greater tendency to fatty changes. Nevertheless, it seems best for the present to reserve the term acute yellow atrophy to that form of liver necrosis and autolysis

which occurs "idiopathically," and which presents certain features different from chloroform necrosis, puerperal eclampsia and phosphorus poisoning, and which is possibly due to some specific cause. The fact that chloroform seems particularly to affect livers in which fatty degeneration has been previously produced by some other disorder, may possibly be due to the known absorption of chloroform by intracellular fats, which in this case would increase the concentration and duration of action of the chloroform in the degenerated liver cells. Chloroform is a violent protoplasmic poison and, if it were to inhibit or destroy the oxidizing enzymes of the liver cells, the results would presumably be quite the same as those characteristic of chloroform necrosis; hence it seems probable that chloroform produces its effects by acting on the oxidizing enzymes, without corresponding inhibition of the autolytic enzymes and the lipase of the cells.

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MORPHOLOGY OF THE BLOOD IN PERTUSSIS.*

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HISTORICAL.

To Frölich[1] of Breslau belongs the credit of having first called attention to the blood in pertussis. During an epidemic of this disease in the summer of 1897, he examined the blood in fifty-five cases, making total leucocyte counts in all the cases and differential counts in fifteen. In one case he made three counts during three consecutive weeks and in another two counts; in all the other cases the patients were examined but once.

Summarizing his results, he says, in conclusion, that in this disease there is a constant leucocytosis and lymphocytosis which in individual cases may show high values. The highest counts were noted when the number and severity of the coughing spells reached their maximum, and with the disappearance of these the leucocytosis disappeared. He considered, however, that the blood examination would be of no great value because the changes can not be shown early enough in the disease. He also said that complications have no material effect on the number of leucocytes. In making these examinations he was careful to take the blood at a time of day so as to exclude the physiologic digestive leucocytosis.

With the patients making up these fifty-five cases, eight other children were brought to the dispensary by their parents to be treated for whooping-cough; these patients did not have the disease and their blood showed an absence of the characteristic changes.

In 1898 Meunier[2] examined the blood in thirty cases of pertussis, making 102 enumerations and ten differential counts. He says that the leucocytosis reaches a higher figure than in any other non-febrile affection of children. The leucocytosis comes early—in some cases occurring in the catarrhal stage, reaching its height thereafter, diminishing irregularly, and its complete disappearance is not realized until after the end of the whooping period. The leucocytosis is more intense among

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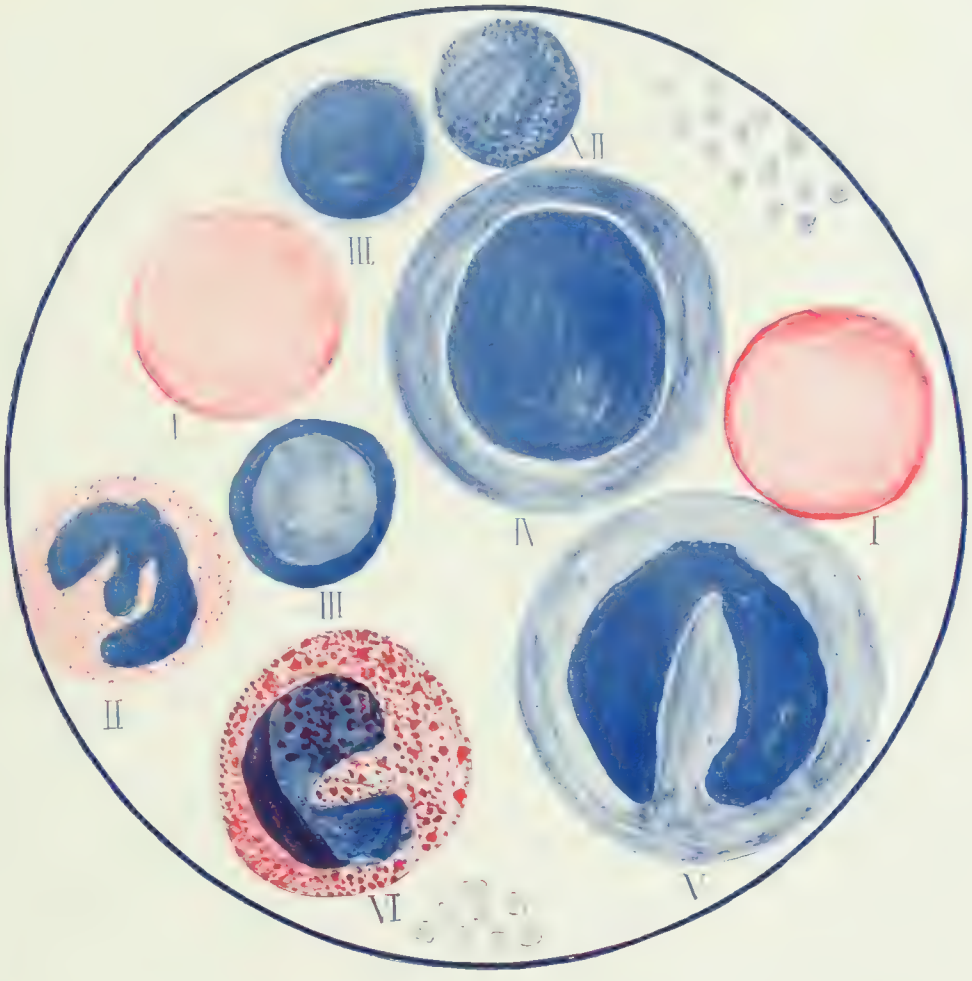
1. Jahr. f. Kindhlk., 1897, xliv, 59.

2. Compt. rend. Soc. de biol., 1898, l, 103.

NORMAL.



I—Red.
II—Poly.
III—Small } Lymph.
IV—Large }

V—Transitional.
VI—Eosinophile.
VII—Mast Cell.
Blood Plates.

infants of 2 or 3 years, and complications have a moderate influence on the count. The increase of the leucocytes, he says, is due to the increase of the lymphocytes, so that the usual blood formula is reversed. During the time of increasing leucocytosis he figures that the polynuclears are doubled, the lymphocytes quadrupled, transitionals tripled and the eosinophiles not affected.

De Amici and Pacchioni,[3] in 1899, examined the blood in eighteen cases. On studying their tables I find that, while in three cases they made more than three examinations in each case, yet not in one instance did they examine the same child in the three stages of the disease. They eliminated digestive leucocytosis. To eliminate a possible mechanical element in the causation of this leucocytosis they put some of the children under partial ether anesthesia so that there would be no spasmodic coughing at the time that the blood was taken—and from their results were satisfied that the spasmodic coughing itself had nothing to do with the cause of the leucocytosis.

From their studies they conclude that there is in the disease a constant leucocytosis which begins early and continues for a long time after the height of the disease. As a rule, in the first and second stages, there will be found more lymphocytes and in the declining stage a prevalence of polynuclears. They also lay stress on the diagnostic value of the blood examination, because these findings are distinctive and different from those of any of the other respiratory affections with which the disease may be confused.

Stengel and White,[4] in 1901, examined three patients with pertussis and found a leucocytosis and lymphocytosis in each of them. Wanstall,[5] in 1903, reports the findings in fifteen cases of pertussis. He made leucocyte counts in but five of these cases and differential counts in all. In examining nineteen children he found that the fifteen patients with pertussis presented more lymphocytes, while the four that proved not to have pertussis showed more polynuclears.

Cases have been reported by Cabot[6] and Stevens[7] in which very high leucocyte counts have been found. Muggia and Bertolotti,[8] in 1904, treated twenty-five patients with pertussis with inhalations of ozone, from which they claimed highly beneficial results. To prove that this

3. Clin. Med. Ital., 1899, xxxiv, 52.
4. Univ. Penn. Med. Bull., 1902, xiv, 318.
5. Am. Med., 1903, v. 62.
6. "Clinical Examination of the Blood."
7. Lancet, 1902, ii, 791.
8. Riv. de Clin. Ped., February, 1905.

benefit was from the antispasmodic action of the ozone rather than from an antitoxic or antimicrobic action, they set about to examine the blood in a number of these cases. Their findings were: Hyperleucocytosis with predominance of mononuclear cells. These predominating cells they classified as large mononuclears. Their object, however, being the study of the effect from the ozone, they say that "ozone does not change the blood formula, and its action is antispasmodic."

It is interesting to note here that in three severe cases they performed lumbar puncture, and found an increased pressure. When from 15 to 20 c.c. of fluid was removed there was a marked clinical improvement, and the fluid contained an excess of lymphocytes.

In 1905 Grulee and Phemister[9] examined the blood in fifteen cases, making one leucocyte and differential count each in the paroxysmal stage of fourteen and one in case at the end of the catarrhal stage. They conclude that there is a leucocytosis in all stages of the disease, increasing with the increasing frequency of paroxysms and decreasing when the paroxysms become less frequent and severe. According to their method of classification, they found that in the one case examined in the catarrhal stage the lymphocytosis was due to the small lymphocytes and in the other cases the lymphocytosis was due to the large lymphocytes.

In 1906 Churchill[10] reported on the examination of thirty-six cases, making leucocyte and differential counts in all. Out of sixteen cases in the catarrhal stage, fifteen of the patients showed a lymphocytosis. In complicated cases he found a reversion of the blood formula from the prominence of the lymphocytes to that of the polynuclears. From his own work and a complete study of the literature, which at that time consisted entirely of 100 cases, he says, in concluding, that from the catarrhal stage on there is a leucocytosis and lymphocytosis which distinguishes this disease from others with which it may be confounded.

Considering all of this evidence, we may deduce therefrom that in this disease a leucocytosis due to the lymphocytes begins in the catarrhal stage of the disease, attains its height in the paroxysmal stage and then gradually declines with the subsidence of the clinical symptoms. Complications may or may not alter the whooping-cough formula; the predominating opinion is that this formula is of value in the diagnosis of the earlier stages of the disease.

This evidence still left much to be desired to a better understanding of the interesting blood change. Nearly all of the cases reported by the above investigators were those of patients brought to the outdoor clinics.

9. Arch. Pediat., N. Y., 1905, xxii, 595-599.
10. Jour. Am. Med. Assn., 1906, xlvi, 1506.

Over these children they had no control and most of them were examined but once. The findings in the catarrhal stage of the disease had to be compared with the findings in the paroxysmal stage of others and with the declining stage of still other children. The personal equation of each case was lost, and the less prominent changes were entirely overlooked.

THE AUTHOR'S CASES.

During the epidemic of whooping-cough which began in January, 1907, I had the opportunity of studying the blood-picture in this disease and endeavored to carry out the work systematically and more extensively than it had been done before. To do this I traced the probable date at which the patients were first exposed, the time when they first coughed, when they began to whoop and when the coughing ameliorated.

TABLE 1.—CONTROL CASES.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	10,370	61.0	30.5	4.5	1.0	3.0
2	2	15,280	73.0	23.0	3.5	0.5	0.0
3	2	11,000	82.5	11.5	5.5	0.5	0.0
4	3	12,600	47.5	45.5	5.5	0.0	1.5
5	3	13,300	66.5	26.5	4.5	0.0	2.5
6	3	11,160	53.5	40.5	3.0	0.0	3.0
7	4	10,720	59.5	34.5	4.0	0.5	1.5
8	4	11,300	28.0	55.0	3.0	1.0	13.0
9	4	10,600	37.5	58.0	1.0	0.5	3.0
10	4	7,250	62.0	27.5	5.5	0.0	5.0
11	4	6,800	48.6	45.6	3.6	0.6	1.3
12	4	10,000	54.6	39.1	3.6	0.3	2.6
13	4	17,000	45.1	41.3	1.6	0.3	11.6
14	4	8,600	39.6	52.4	2.8	0.0	5.2
15	4	12,940	32.5	51.3	4.5	1.8	10.0
16	5	11,200	50.0	42.0	5.0	0.0	3.0
17	5	18,300	46.5	45.5	3.5	0.0	4.5
18	5	11,520	51.0	38.0	4.6	0.6	5.6
19	6	9,500	55.0	35.5	3.0	2.5	4.0
20	6	11,000	60.0	29.5	2.5	0.0	8.0
21	6	14,600	60.0	33.5	4.5	0.0	1.5
22	6	7,000	51.25	39.75	7.75	0.25	1.0
23	6	7,200	61.50	32.5	3.0	0.0	3.0
24	6	10,700	63.0	31.5	3.5	0.5	1.5
25	6	9,000	65.6	28.3	1.6	2.0	1.6
26	6	8,120	61.0	31.5	2.5	1.0	4.0
27	7	10,000	69.0	22.5	3.5	0.0	5.0
28	7	9,000	62.5	26.5	7.0	1.0	3.0
29	7	10,400	71.0	23.0	4.0	1.0	1.0
Average		10,567	55.74	35.92	4.06	0.54	3.7

The cases are thus classified and in almost each instance a typical cycle can be seen to have occurred. In this way I studied the blood in fifty cases, and my findings are uniform enough to assure the value of the blood examination in diagnosis and to establish the blood-picture for the disease.

The children in which the disease occurred were of the usual whooping-cough age, the greater part of them being institution children previously healthy. Although such children often come from the lower walks of life and have hereditary taints and predispositions, and being institution children live in hygienic surroundings not so good as those enjoyed by children in private homes, yet the results were in no way different from those in cases which occurred in the families of the members of the Academy, whose children represent the highest grade of child life.

These facts assure me beyond doubt that the reaction of the organism to the pertussis infection takes place in a definite way and is associatsd with certain specific manifestations. Of these, the change in the blood formula is one feature.

TABLE 2.—AVERAGE AT DIFFERENT AGES.

Age.						
4.....	10.578	45.26	44.96	3.7	0.62	6.6
5.....	10.340	49.0	41.83	4.3	0.2	4.3
6.....	9.640	59.6	31.28	3.5	0.84	3.0
7.....	9.800	67.3	24.0	4.8	0.6	1.5

For the sake of brevity I will tabulate in detail only the first thirty cases of this series; not picked cases, but the first thirty that came under my observation. As may be seen (Table 4) the first twenty-nine cases occurred in children from 1½ to 7 years, inclusive, and the thirtieth case occurred in a lady 72 years of age, the mother of a physician. This case I will mention separately. For the normal controls I have made blood counts in healthy children of the same age, living under exactly the same circumstances (Table 1).

As is well known, during the first seven years of life there is a progressive fall in the number of leucocytes, a gradual decrease in the proportion of lymphocytes, and a simultaneous increase of the polynuclears in the circulatory blood. This is distinctly seen in the table of the control cases, excepting in children of the first three years of life. This error, I believe, is entirely due to the small number of cases included. Table 3 gives the average of the control cases at their relative ages.

THE TABULATED RESULTS.

We might compare the individual cases at their relative ages, but, for the sake of brevity, I have arranged each of these tables with sum-totals and averages, and the results are distinct and characteristic. The blood was taken always before meal time, so as to eliminate digestive leucocytosis.

Table 1 shows the counts in the control cases.

Table 2 shows the average counts of the healthy children at their relative ages.

Table 3 shows the counts in those cases of the series in which the first blood examination was made within the first week of the coughing, at the clinical onset of the disease.

TABLE 3.—AT ONSET.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	30,250	65.3	27.6	4.3	2.0	0.3
10	4	11,760	46.0	47.0	5.0	0.0	2.0
11	4	12,000	69.0	18.5	10.0	1.0	1.5
12	4	17,600	54.5	39.0	4.0	0.0	2.5
13	4	28,000	47.5	41.0	4.5	3.0	4.0
15	4	18,100	49.0	41.0	9.0	1.0	0.0
17	4	9,750	35.0	52.0	6.0	3.0	4.0
20	6	15,660	37.3	52.6	5.1	2.0	3.0
22	6	7,300	47.5	45.5	3.0	0.5	3.5
23	6	33,000	71.0	19.0	4.0	0.5	5.0
24	6	10,500	31.5	53.5	7.5	3.0	4.5
25	6	16,000	40.0	52.0	3.0	3.0	2.0
26	6	12,050	43.0	43.0	5.0	0.0	9.0
29	7	23,800	63.0	31.0	4.0	1.0	1.0
Average.....		17,539	50.06	40.19	5.02	1.42	3.02

TABLE 4.—AT HEIGHT.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	20,400	49.0	42.0	8.0	0.5	0.5
2	2	40,400	27.5	65.5	4.5	0.5	2.0
3	2	32,250	31.5	65.0	1.5	1.5	0.5
4	2	14,880	33.0	48.5	13.5	1.0	4.0
5	2	88,300	27.5	67.5	3.25	0.25	1.5
6	3	21,200	28.0	60.0	5.0	0.5	6.5
7	3	42,720	24.5	69.0	4.0	0.5	2.0
8	4	36,600	34.5	59.5	4.0	1.0	1.0
9	4	13,300	37.0	52.5	8.0	1.0	1.5
10	4	10,220	47.0	39.0	7.0	1.0	6.0
11	4	25,800	50.0	44.5	3.5	0.0	2.0
12	4	10,800	54.0	38.0	5.5	1.0	1.5
13	4	32,250	37.0	59.5	1.5	0.0	2.0
14	4	14,280	35.5	49.0	12.0	0.5	3.0
15	4	26,240	50.0	46.0	2.5	0.0	1.5
16	4	10,500	35.0	49.0	5.0	0.0	11.0
17	5	15,000	47.5	44.0	4.0	1.5	3.0
18	5	11,850	49.0	41.5	7.0	0.5	2.0
19	6	10,800	40.0	47.0	8.0	1.0	4.0
20	6	41,750	41.6	54.6	3.3	0.3	0.3
21	6	16,200	45.5	39.0	7.5	0.5	7.5
22	6	23,500	38.0	47.0	7.0	2.0	6.0
23	6	13,280	27.0	57.0	9.0	0.0	7.0
24	6	49,280	33.0	62.0	3.0	1.0	1.0
25	6	9,400	44.0	41.0	9.0	2.0	4.0
26	6	9,700	30.0	50.0	13.0	2.0	5.0
27	7	13,300	33.5	53.5	4.0	1.0	8.0
28	7	20,000	29.0	60.0	7.0	1.0	3.0
29	7	34,160	49.0	45.0	3.5	1.0	1.5
30	72	7,000	32.0	50.0	9.0	1.0	8.0
Average.....		22,512	38.06	51.52	6.10	0.78	3.56

Table 4 shows the counts at the height of the disease in the spasmodic stage. The highest counts are seen in those patients who my notes show to have been the sickest children.

Table 5 shows the counts in those cases in which clinically the patients showed a marked improvement. The average time in which the coughing subsided was two months and eleven days.

TABLE 5.—MARKED IMPROVEMENT.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	5,000	44.0	45.0	6.0	2.0	3.0
2	2	10,500	56.0	27.0	1.0	1.0	15.0
3	2	9,200	45.0	38.0	11.0	3.0	3.0
4	2	12,000	38.0	47.0	4.5	0.5	10.0
5	2	20,200	40.0	52.0	5.5	1.0	1.5
6	3	10,400	44.0	42.5	8.0	1.0	4.5
7	3	6,200	50.0	48.0	1.0	1.0	0.0
8	4	15,500	51.0	34.0	5.5	0.0	9.0
9	4	7,500	42.0	53.0	2.0	1.0	2.0
10	4	6,600	48.0	40.0	4.0	2.0	6.0
11	4	9,400	45.5	44.0	2.0	2.5	6.0
12	4	13,860	60.0	29.5	5.0	2.5	3.0
13	4	11,700	47.0	42.0	6.5	1.0	3.5
14	4	12,200	45.0	47.0	4.0	0.0	4.0
15	4	13,300	48.3	45.0	2.6	0.0	4.0
16	4	7,800	61.0	29.0	6.0	0.0	4.0
17	5	14,200	42.0	42.5	6.0	1.0	8.5
18	5	8,500	50.0	40.0	5.0	1.0	4.0
19	6	10,000	57.5	33.0	2.5	0.5	6.5
20	6	11,750	55.0	35.0	6.0	0.0	3.5
21	6	8,160	49.0	40.0	2.0	4.0	5.0
22	6	11,320	49.0	38.0	3.0	2.0	8.0
23	6	10,200	35.0	49.0	10.0	0.0	6.0
24	6	7,600	37.0	44.0	8.0	2.0	9.0
25	6	8,460	48.0	38.0	6.0	2.0	6.0
26	6	7,800	45.5	42.5	6.5	1.0	4.5
27	7	12,000	48.5	38.0	5.0	1.0	7.5
28	7	9,000	55.0	40.0	2.0	0.0	3.0
29	7	15,428	77.0	18.0	3.0	0.0	2.0
30	72	8,250	57.0	27.5	3.5	3.5	8.5
Average.....		10,451	49.5	39.61	5.1	1.21	5.35

Table 6 shows the counts in the same children after they had been in the country from June to October; at the end of that time they were comparatively in good health.

THE BLOOD-COUNT.

I will now consider the various elements in the blood-count and the course that they pursued. The control will be Table 4.

The Leucocytes as a Whole.—Within a week of the first cough there is a marked leucocytosis, before the change in the differential formula is really noticeable. The leucocytosis steadily increases, reaches its height

in the spasmodic change and then falls by lysis. The average time in which the leucocytes returned to about their normal number was three months and fifteen days after the onset.

The Polynuclears.—Relatively they seem to fall in number, but absolutely they are increased in a moderate degree.

TABLE 6.—EIGHT MONTHS LATER.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	10,560	54.5	36.5	3.5	0.5	5.0
2	2	10,800	41.0	49.5	3.0	0.5	6.0
3	2	13,800	50.5	41.5	4.5	1.0	2.5
4	2	11,600	50.0	36.5	3.5	0.5	9.5
5	2	.....	.....	.....	.....	.....	.....
6	3	9,500	57.5	29.0	3.5	3.0	7.0
7	3	.....	.....	.....	.....	.....	.....
8	4	8,600	57.0	36.0	2.0	1.0	4.0
9	4	6,800	56.0	40.0	3.0	1.0	0.0
10	4	8,800	66.0	25.0	5.0	2.0	2.0
11	4	14,300	57.0	35.0	1.5	0.5	6.0
12	4	12,200	50.0	40.0	2.0	1.0	7.0
13	4	7,800	56.0	35.0	0.0	1.0	8.0
14	4	10,500	69.0	25.0	4.5	1.0	0.0
15	4	20,750	55.5	40.5	2.5	0.0	1.5
16	4	9,060	68.0	24.0	5.0	2.0	1.0
17	5	6,200	47.5	39.5	4.5	0.0	8.5
18	5	10,900	71.0	21.0	5.0	2.0	1.0
19	6	9,300	49.5	37.0	3.0	1.0	9.5
20	6	8,500	47.0	41.0	3.5	0.5	8.0
21	6	9,200	70.0	20.0	5.0	1.0	4.0
22	6	14,300	61.0	21.0	6.0	1.0	11.0
23	6	9,800	63.0	18.0	4.0	4.0	11.0
24	6	11,600	69.0	24.0	2.0	1.0	4.0
25	6	10,600	72.0	19.0	7.0	0.0	2.0
26	6	.....	.....	.....	.....	.....	.....
27	7	.....	.....	.....	.....	.....	.....
28	7	1,300	59.0	27.0	5.0	0.0	9.0
29	7	12,100	62.0	32.0	5.0	0.0	1.0
30	72	.....	.....	.....	.....	.....	.....
Average		10,355	58.0	32.0	4.0	1.0	5.0

The Small Lymphocytes.—These are the most prominent elements in the blood change. Their increase begins early in the disease, at times, I believe, before the child coughs. From that time on they continue increasing in number and reach their height in the spasmodic stage. Their fall is gradual, by lysis, and they reach their normal numbers in about three and a half months.

The Large Lymphocytes.—These follow nearly the same course as do the small variety. They increase from the onset, reach their height in the spasmodic stage and decrease thereafter. I did not find that their number was highest in the cases that had the highest grade of small cell

lymphocytosis, nor *vice versa*. In one case a count showed 18 per cent. This was the highest. Nothing else could be associated with it either in the blood-picture or clinically. On carefully studying these cells I find that their numbers are highest at a period which does not exactly coincide with that at which the small lymphocytes are most numerous; it appears to be slightly later. This might mean that these cells represent the final reaction of the lymphocytes or perhaps of the tissues from which these cells are derived, to the pertussis infection. While it is Table 4 that shows their highest numbers, yet that is not the time when they reached their greatest height. These tables show only four of the average number of eight counts that were made in each case.

The Transitionals.—The course of these cells seemed very irregular. They were distinctly less numerous during the height of the lymphocytosis, and comparison with each of the other elements at the different stages of the disease reveals nothing.

The Eosinophiles.—The rôle played by the eosinophiles is distinctive. At the beginning and during the lymphocytosis they are present in about their normal proportions. Somewhere near the third month of the disease, at about the time of recovery, an eosinophilia begins and may continue for several months. In Table 5, which represents the time of marked improvement, out of the thirty cases, twenty of the patients had an eosinophilia averaging 6.75 per cent. Of the remaining ten cases, seven of the patients showed an average count of 8.16 per cent. on the examination immediately before or after the time of the examination in the other cases. This leaves but three cases out of the thirty that at the time of recovery did not present an eosinophile count distinctly above the normal.

On studying the control table (Table 1) we find that the apparently healthy children present a variation of from 1 to 13 per cent. of eosinophiles. Yet the regularity with which the increase of eosinophiles above their normal average proportion occurs in the disease at the time of recovery leads me to believe that the eosinophile has a part of its own in this blood cycle.

These are the more commonly recognized elements of the differential blood count, but in these examinations I have often seen other cells that are worthy of mention.

Mast Cells.—These were conspicuously noted in thirty-eight out of fifty cases and they never exceeded 4 per cent. Their relationship was as follows:

To the total leucocyte count they bore no relation.

To the polynuclears and small mononuclears: Out of thirty-eight cases, at the time when the mast cells were noted, twenty-three showed a greater number of polynuclears; the other fifteen cases showed more small lymphocytes.

To the large lymphocytes: Their presence was noted more frequently about the time the large lymphocytes were high.

To the transitionals: No relation.

To the eosinophiles: No distinct relation, but they occurred more often when the eosinophiles were above the normal.

On the whole, we find that they were more frequent about the time of recovery.

Bilobate Small Lymphocytes.—These cells were very often present, during the stages of active lymphocytosis, which means during the first three or four weeks of the infection.

Degenerated Large Lymphocytes.—The large "basket forms" and smaller forms were also frequently seen during the active lymphocytosis.

Myelocytes with eosin and basophile granules were occasionally noted.

Basophile cells, containing both basophilic and eosinophilic granules, were also noted several times.

Blood plates were seen in very large numbers in two cases after crises from pneumonia complicating the disease. This is the so-called *crise hémotoblastique* of Hayem, who says that the occurrence of large numbers of plates comes with the recovery from the disease (pneumonia). In none of the other cases were they seen in large numbers, although they were always present.

THE ADULT CASE.

The adult case which occurred in a lady 72 years of age was clinically unmistakable. She had the disease at the same time that her three grandchildren were having it. The first count was made during the spasmodic stage and the following ones according to given dates. There was no leucocytosis in this case, but the formula was distinctly reversed. See Table 8.

COMPLICATIONS.

Complications have their effect on the blood formula in a very characteristic way. As will be seen (Table 7) the respiratory organs were most commonly involved and the complications were as follows: Two cases of bronchopneumonia, two cases of pleuropneumonia and one case of suppurative otitis media.

Table 7 shows the effect on the blood formula in each instance. In the pneumonias, the leucocytosis was increased and the polynuclears be-

came at once the prominent cells. As soon as the pneumonias subsided, the leucocytes fell and the lymphocytes became prominent, a reversion to the pertussis formula. De Amici and Pacchioni,[3] Cabot[6] and Churchill[10] report cases complicated by pneumonia, and their findings seem at variance.

TABLE 7.—COMPLICATIONS.

Date.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
CASE 1. BRONCHOPNEUMONIA.						
Feb. 9, 1907	49,280	33.0	62.0	3.0	1.0	1.0
Feb. 14, 1907	64,000	49.0	41.5	8.0	0.5	1.0
Feb. 25, 1907	32,000	39.3	54.3	6.0	0.0	0.3
March 10, 1907	13,800	60.0	31.0	5.5	1.0	2.5
CASE 2. BRONCHOPNEUMONIA.						
Feb. 5, 1907	7,300	47.5	45.5	3.0	0.5	3.5
Feb. 20, 1907	18,250	66.0	21.0	5.0	2.6	4.0
Feb. 28, 1907	16,200	45.5	39.0	7.5	0.5	7.5
CASE 3. PLEUROPNEUMONIA. DIED.						
Jan. 26, 1907	39,000	37.0	56.0	4.5	1.0	1.5
Feb. 2, 1907	62,750	53.0	34.5	9.0	1.5	1.5
Feb. 18, 1907	74,000	70.8	22.0	5.5	0.8	0.16
CASE 4. PLEUROPNEUMONIA.						
Jan. 18, 1907	38,800	28.7	65.4	4.53	0.58	0.8
Jan. 24, 1907	53,000	60.3	36.6	2.6	0.3	0.0
Feb. 3, 1907	19,800	30.0	57.5	11.0	1.5	0.0
CASE 5. SUPPURATIVE OTITIS MEDIA.						
Jan. 26, 1907	30,250	65.3	27.6	4.3	2.0	0.3
Jan. 31, 1907	19,830	47.5	41.5	7.5	2.5	1.0
Feb. 26, 1907	10,250	32.0	42.0	18.0	3.0	5.0

TABLE 8.—ADULT CASES.

Date.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
March 4, 1907	7,000	32.0	50.0	9.0	1.0	8.0
March 12, 1907	7,700	53.0	38.5	5.0	0.5	3.0
April 18, 1907	8,250	57.0	27.5	3.5	3.5	8.5

A number of the patients in these fifty cases during the paroxysmal stage were sick enough to be put to bed. At these times I examined their chests when I took the blood specimens, and from those observations my belief is that so long as there exists but a severe bronchitis with perhaps small areas of consolidation the lymphocyte formula will be retained, but just as soon as a distinct consolidation is present the formula will be reversed and the polynuclears will predominate.

In the case of suppurative otitis media, the complication was present when the first count was made at the onset of the whooping-cough; after

the ear was drained, the leucocyte count at once fell and the cells assumed the characteristic formula.

In five cases the patients gave a history of having had the disease before. They were patients in Cases 10, 22, 23 and 30. Of these, the patient in Case 10 did not show a lymphocytosis; the others were typical.

SUMMARY.

After a careful study of these cases individually and in the aggregate, in which on an average eight leucocyte and differential counts were made in each case, at regular intervals, the blood cycle in this disease appears to occur as follows:

There is at first a leucocytosis with increase of all the forms; then a small cell lymphocytosis becomes conspicuous and continues to increase when the other forms have reached their limit. The large lymphocytes follow the course of the small ones, but they reach their greatest numbers after the small cells have reached theirs. During the stage of active lymphocytosis, bilobed small lymphocytes are frequently seen as well as numerous degenerated large lymphocytes, especially the basket forms.

Then comes the simultaneous falling of the leucocytosis and lymphocytosis, while the polynuclears begin to resume their normal proportion. A little later the mast cells are observed more frequently, and an occasional myelocyte may be seen. While the leucocytosis and lymphocytosis continue to fall by lysis, an eosinophilia is noted; this continues for a variable time, after which the blood formula resumes its normal proportions. During this entire cycle the transitionals seem unaffected.

If we were to speak of the first and second half of the blood cycle in this disease, we would say that in the first half the lymphocytes are the prominent factors and in the second half the polynuclears and the eosinophiles.

Clinically, leucocytosis is present at about the time the child first coughs; as the coughing goes on, the leucocytosis increases and the lymphocytosis becomes very marked. A glance at the tables gives an idea of the numbers. The height of the leucocytosis is reached in the spasmodic stage, sometimes early, and sometimes in the latter part, the sickest children showing the highest grade of leucocytosis. About the time that a marked improvement is noted in the child the leucocytosis has decreased, the polynuclears have increased and the eosinophilia is present. This eosinophilia continues for a variable time.

Little more need be said of the distinct value of blood examination in the early diagnosis of the disease. Within the last two months I have

been able to make correctly for other physicians three negative and two positive diagnoses before clinical signs were decisive.

I wish to express my thanks to Dr. Ewing W. Day, Dr. T. J. Elterich, Dr. P. J. Eaton and Dr. Lawrence Litchfield for the clinical material that they have placed at my disposal in carrying on this investigation, and to Dr. E. G. Matson and Dr. G. Conti for their kind assistance in translating the original articles from which I have quoted in the first part of this paper.

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EXPERIMENTS WITH AN ASH-FREE DIET.*

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The introduction of standard test diets into clinical medicine has distinctly advanced our knowledge of human metabolism and furnished many useful data for diagnosis, prognosis and treatment. Such are the Ewald test breakfast, the diet of Schmidt and Strassburger for the study of diseases of the gastrointestinal tract and the proteid-fat diet employed in diabetes. Although these various diets were excellent, they threw light on only the more superficial phenomena of metabolism, and it was to be expected that other variations in the diet would be planned which would penetrate into the more fundamental processes of the body. It is to the credit of Taylor[1] that he devised such a diet in 1904 and had the temerity to live on it until unusual symptoms occurred.

Admirable as was the conception and interesting as were the results of Taylor's experiments with an ash-free diet, one of his observations and the interpretation he later placed on it were so at variance with prevailing ideas as to attract our attention. He writes: "On the ninth day a colleague noted in the breath a strong odor of acetone. Investigation thereon revealed in the urine notable quantities of acetone and diacetic acid without β-oxybutyric acid." At the session of the Association of American Physicians held in 1907 this observation was cited by Taylor as an argument against the generally accepted theory of acidosis of the β-oxybutyric type, which ascribes its occurrence to the lack of oxidation of carbohydrates in the metabolism. His criticism apparently was fully justified, because, according to his experiment, an acidosis developed in a healthy individual on a diet which maintained equilibrium and contained 200 grams of carbohydrates which were known to be assimilated.

The overthrow of any theory which has served so many useful purposes as the secondary oxidation theory proposed by Nasse and adopted by Naunyn can hardly be considered accomplished by a single experiment. It, therefore, seemed well worth while to repeat the work, particularly because, so far as we are aware, no further evidence has been offered which would confirm it. The mere detection of acetone in the breath by

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1. Taylor: Studies on an Ash-free Diet, Univ. of Calif. Pub., Pathology, 1904, i, p. 71.

the sense of smell can not be accepted as a sufficient guarantee of its presence. Indeed, Folin's recent observations[2] make it probable that the so-called "acetone breath" has nothing to do with acetone. The actual quantity of acetone in the urine is not given by Taylor, but at the most the acidosis must have been slight, because the ammonia-nitrogen nitrogen ratio reached but 9.5 per cent. Convincing proof that acidosis of the acetone type was due to the withdrawal of salt might have been afforded if an acidosis thus produced had disappeared on the addition of salt to the diet without other change in the plan of the experiment.

Our experiments followed exactly the methods suggested by Dr. Taylor. Two healthy medical students, Mr. Sawyer and Mr. Smith, consented to act as subjects.[3]

The daily diet consisted of the whites of 18 eggs, 120 gm. olive oil, and 200 gm. of crystallized sugar. The albumin was prepared in the following manner: Eighteen hundred c.c. distilled water (100 c.c. to the white of each egg) were heated in a double boiler up to 56 degrees C. The whites of the eggs, previously broken up with a glass rod until homogenous, were then poured in, and at first stirred briskly, but later more slowly until the temperature reached 100 degrees C. Twelve c.c. of acetic acid, diluted by one-fifth, were added and the clear fluid decanted off from the precipitated albumin. The precipitate was thoroughly mixed with 1,000 c.c. distilled water, heated nearly to the boiling point and again decanted, this procedure being repeated three times. The albumin was then transferred to a large Buchner filter and again washed three or four times with hot distilled water. The final filtrate was nearly free from chlorin. The sugar was given in the form of rock candy, of which the ash was non-weighable. The olive oil was washed half a dozen times in a large separating funnel with distilled water. Distilled water alone was drunk and in measured quantities.

Bone-black was used in the demarcation of the stools and was taken with the last regular meal, which was twelve hours before the commencement of the experiment, and again on its completion just before a return to an ordinary diet.

The first experiment was begun Nov. 29, 1907, and continued for thirteen days. Mr. Sawyer's observations during this period are given in his own words. He writes:

2. Folin, Otto: Chemical Problems in Hospital Practice. Jour. Am. Med. Ass'n., 1908, l, p. 1391.

3. Mr. Sawyer and Mr. Smith lived at the New England Deaconess Hospital during the course of the experiment, and to that institution we are much indebted for the many courtesies we received.

The albumin was the most disagreeable part of the diet. I used a syrup with this so as to give it a taste, and in this way it was more easily swallowed, but to the end this proved to be the most irksome part of the experiment. During the time of the dieting I worked between seven and eight hours at the school, at least half of which time I was standing. I spent about two hours of each of the two Sundays that intervened in walking. I slept longer than I usually do, averaging about nine and one half hours in the day. There were two nights, however, during which I lost about three hours on account of indigestion. With the loss in weight there was also loss in strength, and I found myself more easily winded and more easily tired. On some of the evenings of the more strenuous days I was quite exhausted. On two occasions I had a slight fainting attack. Three evenings before the termination of the experiment I had some symptoms of indigestion, namely, the distress from abdominal distension, hiccough and some belching of gas. My appetite throughout was good, at times ravenous, but not for the ash-free diet, to which I never looked forward. What discomfort there was to the experiment did not progress from first to last. Some of the days earlier in the experiment were more trying than the last.

The diaphoresis which Dr. Taylor observed throughout was noted neither by Mr. Sawyer nor observed by us. Mr. Sawyer's symptoms were not progressive in character, and in this respect he differed both from Dr. Taylor and Mr. Smith. The daily quantity of chlorin in the urine steadily decreased, and on the tenth day reached 0.22 gm., but as the breath and urine gave no evidence of the presence of acetone or diacetic acid the experiment was continued. On the eleventh day the chlorin remained the same, but on the twelfth day it fell to 0.17 gm., or 0.02 gm. less than the lowest limit reached by Taylor. Tests for acetone and diacetic acid still being negative, the diet was continued for another twenty-four hours. The chlorin on this, the thirteenth, day was the same as on the twelfth, but acetone and diacetic acid still failed to appear, and the experiment was, therefore, discontinued. On two subsequent days, namely the second and fourth, the urine was again collected.

The reaction of the urine was acid throughout, and daily tests failed to reveal the presence of albumin, sugar or, as already recorded, acetone or diacetic acid. Le Nobel's test was used for the determination of acetone, and Gerhardt's ferric chlorid test for the diacetic acid. With few exceptions these were performed in the presence of Dr. Folin. The color of the urine was uniformly normal for the first nine days, but became slightly high on the tenth and eleventh and distinctly high on the twelfth and thirteenth. Indican was present in variable quantities as shown qualitatively, gradually decreasing from the first to the sixth day, and then gradually increasing up to the end of the experiment. The urinary sediment gave no evidence of disease of the kidneys. Tables 1, 2, and 3 give the analytical details. The nitrogen was estimated by

the Kjeldahl method, and the ammonia, creatinin, sulphates and total sulphur by the Folin method.[4]

The weight of the dried feces was 121.68 gm., or about 9.0 gm. per day. This is two or three times the weight of the feces of a starving individual. The total quantity of fat in the feces amounted to 53.2 gm., and as the total fat in the diet was 1,560 gm. the total quantity of fat absorbed was 96.6 per cent. The total nitrogen in the feces was 6.05 gm. If the total nitrogen in the diet for the thirteen days is estimated at (11.5 x 13 =) 150 gm., the percentage of nitrogenous food absorbed was 96.

The excellent absorption of the protein and fat is striking and deserves emphasis. It is a most useful point to bear in mind in the treatment of patients. So much has been attributed to the psychic phenomena of digestion that it is well occasionally to have proof that an uninviting and positively distasteful diet, which does not awaken the least suspicion of an appetite, may be thoroughly assimilated.

It is evident from the table that Mr. Sawyer was in nitrogenous equilibrium, because the total nitrogen for the thirteen days was nearly constant, varying from a maximum of 10.7 gr. to a minimum of 12.18 gr., the daily average being 11.5 gm.

The chlorin is the center of interest, because this inorganic salt comprises such a large percentage of the inorganic salts in the urine, and further because of the importance which recent work has assigned to it in metabolism. Its gradual diminution during the thirteen days is mathematical proof of the accuracy of the experiment. The amount of chlorin excreted, 12.94 gm., corresponds to the figures which were obtained in the experiments on Cetti and Breithaupt and those of Belli and Wundt. In the first two days more salt was excreted than in the remaining eleven days, a striking proof of the tenacity with which the body retains its chlorin. For the last five of the thirteen days of the experiment the excretion was practically constant at 0.2 gm. The data show well the limitations of the withdrawal of salt, and again furnish proof that only about 15 per cent. of the total chlorin in the body can be removed. On the conclusion of the experiment Mr. Sawyer returned to his ordinary diet, eating, however, with moderation. Two days later the total quantity of chlorin excreted was only 3.5 gm., despite the fact that he had used rather more salt than was customary, but after four days of the ordinary diet the chlorin amounted to 25.76 gr., and the quantity of urine reached a total of 4,090 c.c. For this great increase

4. Folin: Jour. Biol. Chem., 1906, i, 131.

in the excretion of salt and water we have no explanation, and speculation is unprofitable because of the unknown character of the ingesta. In the next experiment we attempted to follow this point more closely.

The weight can be brought into connection with the chlorin because the two varied together. Sawyer lost 2.8 kg. during the first three days of the experiment, but in the remaining ten days only 2.5 kg. Taylor reports a loss of 1.5 kg. "during the period." Probably this statement refers to the change in weight from his third to ninth day. Quite as striking as the loss of weight during the experiment was the gain of 4.1 kg. in the first seventy-two hours following its completion. Whereas the addition of salt to the diet of a healthy person has little effect due to its ready elimination, the withdrawal of salt from the diet is of more significance, because along with it goes a lowering of body weight by removal of water. This fact must always be borne in mind in any experiment in which weight is a factor.

The loss of 10 per cent. of body water is said to produce a moribund condition in thirsting animals, but the conditions of our experiment were different in that the loss of water was coincident with the loss of salt, and so in a way physiologic.

The intake of water was nearly constant, diminishing slightly as the experiment progressed. The possibility that this diminution in the supply of fluid was concerned in the loss of weight was excluded in the second experiment by keeping the intake of water at a constant level of 2,000 c.c. Less fluid was voided than water drunk, corresponding to the well-known fact that a considerable percentage of the water excreted passes out by the lungs and skin. Thirst was not a symptom in the experiment, and, indeed, would appear to vary with different individuals. Thus Taylor (weight 80 kg.) desired over two liters of water daily, Sawyer (weight 70 kg.) was comfortable with 1,300 c.c., and Smith (weight 55 kg.) found only a little less than two liters sufficient. No constant relation can be drawn between the intake of water and the excretion of urine in this experiment.

A steady diminution in the excretion of phosphoric acid took place, but this was not as marked as was the decrease in chlorin. Our values for phosphoric acid are calculated as P_2O_5, while Taylor's are estimated in terms of PO_4. The actual quantity of phosphorus excreted, therefore, was a trifle lower in Sawyer's case than in Taylor's experiment.

The quantity of ammonia was fairly constant from beginning to end, varying from 0.94 gm. on the first day to 1.26 gm. on the tenth. The ammonia-nitrogen nitrogen ratio was nearly uniform throughout. In percentage as well as in absolute quantity it was, however, slightly higher

than the results recorded by Folin.[5] This is readily accounted for by the fact that in our experiment the alkalin salts of the egg whites have been removed.

The creatinin was the most constant factor of all, the lowest quantity being 1.47 gm. and the greatest 1.6 gm. The percentage of creatinin-nitrogen to the total nitrogen varied from 4.6 to 5.4. This percentage is greater than Folin found to be the case with his normal diets, but less than that of healthy individuals on his cream-starch diet. This variation in percentage is accounted for by the total protein of the ash-free diet being considerably lower than that of the standard diet and greater than that of the cream-starch diet. The total quantity of creatinin, however, was practically the same; thus Folin found the average for thirty normal urines to be 1.55 gm. creatinin, and the average in Sawyer's case was 1.54 gm. This is identical with the calculated value for creatinin for an individual of Sawyer's weight, namely 1.54 gm. (22 mg. creatinin per 70 kg. body weight), a further illustration of its dependence on body protein rather than on the protein of the food.

TABLE 1.—INTAKE OF WATER, URINARY ANALYSIS, WEIGHT.

Day.	H_2O	Urine	Sp.	P_2O_5	Cl.	Weight
	c.c.	c.c.	Gr.	gm.	gm.	kg.
1	1470	1720	1012	1.29	4.60	70.2
2	1550	1810	1010	1.29	2.52	...
3	1560	1430	1012	1.28	1.88	...
4	1290	930	1017	1.20	0.87	67.4
5	1290	1100	1013	1.43	0.69	...
6	1545	1170	1012	1.04	0.48	66.6
7	1200	850	1015	1.15	0.46	...
8	1125	1000	1013	0.78	0.40	66.1
9	1290	1160	1011	0.95	0.26	...
10	1200	860	1015	0.89	0.22	...
11	1260	650	1018	0.76	0.22	...
12	1215	510	1023	0.79	0.17	65.1
13	1170	560	1023	0.86	0.17	64.9
14	....	....	....	...	...	...
15	....	940	1029	...	3.50	...
16	....	....	....	...	...	69.0
17	....	4090	1017	...	25.76	...

The uric acid nitrogen was also practically constant, but the percentage was considerably lower than found by Folin in his normal urines. This is in conformity with his idea that the actual amount of uric acid diminishes along with the diminution of the total nitrogen, even apart from the purin nitrogen of the food.

5. Folin, Otto: Approximately Complete Analyses of Thirty "Normal" Urines, Am. Jour. Physiol., 1905, xiii, 45; Laws Governing the Chemical Composition of Urine, Am. Jour. Physiol., 1905, xiii, 66.

The urea represents the chief variable in nitrogenous metabolism. It was low in this experiment, due undoubtedly to the constancy of the excretion of creatinin and the diminution in total nitrogen. Our values for the undetermined nitrogen correspond to those usually found.

TABLE 2.—NITROGEN METABOLISM IN EXPERIMENT ON SAWYER.

Day.	Total—N.	Urea—N	Ammonia—N	Creatinin—N	Uric Acid—N	Undetermined N	Urea—N	Ammonia—N	Creatinin—N	Uric Acid—N	Undetermined N
	gm.	gm.	gm.	gm.	gm.	gm.	P.C.	P.C.	P.C.	P.C.	P.C.
..	....	*20.7*	0.94	*1.60*	*0.18*	...	...	..	..	..	..
1	11.49	9.66	0.78	0.58	0.06	0.41	84.1	6.8	5.0	0.5	3.6
..	...	*18.*	1.02	*1.47*	*0.16*	...	...	..	..	..	..
2	10.27	8.39	0.85	0.55	0.55	0.43	81.7	8.3	5.4	0.5	4.1
..	....	*20.6*	1.04	*1.58*	*0.20*	...	...	..	..	..	..
3	11.67	9.62	0.87	0.59	0.06	0.53	82.5	7.5	5.0	0.5	4.5
..	....	*18.8*	1.12	*1.51*	*0.22*	...	..	.	..	..	..
4	10.73	8.75	0.93	0.56	0.07	0.42	81.5	8.7	5.2	0.7	3.9
..	....	*18.9*	1.13	*1.56*	*0.22*	...	...	..	..	..	..
5	10.86	8.81	0.94	0.58	0.07	0.46	81.1	8.7	5.4	0.6	4.3
.	..	*19.1*	1.17	*1.53*	*0.21*	...	...	..	..	..	..
6	10.91	8.74	0.97	0.57	0.07	0.56	80.1	8.9	5.3	0.7	5.0
.	...	*19.4*	1.15	*1.54*	*0.19*	...	...	..	..	..	..
7	10.72	8.84	0.96	0.57	0.06	0.29	82.5	9.0	5.3	0.6	2.7
.	...	*22.7*	1.24	*1.50*	*0.21*	...	...	..	..	..	..
8	12.18	10.02	1.03	0.56	0.07	0.50	82.0	8.5	4.6	0.6	4.3
..	....	*21.2*	1.24	*1.59*	*0.22*	...	...	..	..	..	..
9	11.86	9.65	1.03	0.59	0.07	0.52	81.4	8.7	5.0	0.5	4.4
	....	*20.7*	1.26	*1.51*	*0.20*	...	...	..	..	..	..
10	11.54	9.23	1.05	0.56	0.06	0.64	80.0	9.1	4.8	0.5	5.6
..	...	*17.9*	1.15	*1.55*	*0.19*	...	...	..	..	..	..
11	10.07	8.16	0.96	0.58	0.06	0.31	81.0	9.6	5.8	0.6	3.0
..	....	*18.8*	1.24	*1.51*	*0.16*	...	...	..	..	..	..
12	10.99	8.77	1.03	0.56	0.05	0.58	79.8	9.3	5.0	0.5	5.4
..	....	*20.9*	1.21	*1.51*	*0.16*	...	...	..	..	..	..
13	11.69	9.37	1.01	0.56	0.05	0.70	80.4	8.6	4.8	0.4	5.8

The total sulphur in the urine was only about one-third that excreted by individuals living on the stardard normal diet. This must be borne in mind in the interpretation of the results obtained for inorganic and ethereal sulphates and neutral sulphur. The ethereal sulphates diminished in the same proportion as the total sulphur with the result that the percentage of ethereal sulphates remains the same as that obtained for the healthy man on the stardard normal diet. The actual quantity of neutral sulphur, however, did not decrease but stayed practically unchanged. As a result the percentage of neutral sulphur in the urine rose from the usual average of 5 to an average of 15.3. Neutral sulphur thus behaves in a similar manner to creatinin. Our results approximate those obtained by Folin in his experiments with the low pro-

tein or starch and cream diet. The inorganic sulphates are here the variable which offsets the increased percentage of neutral sulphur.

Our first experiment thus failed to confirm Taylor's observation on the influence of a salt-free diet on the production of acetone. The question thus stood simply one experiment against another, and it seemed wise to perform a third under slightly different conditions to eliminate the personal equation. The subject, Mr. Smith, weighed much less than either Dr. Taylor or Mr. Sawyer, namely, 55 kg. The experiment was begun on February 15 and ended February 26, but for four days previous to it Mr. Smith lived on a diet poor in salt. By means of this preliminary and partially salt-free period several days were saved and we were enabled to study the effect of the addition of salt in the latter part of the experiment without too great prolongation of the same. The plan was successful, for on the first day the chlorin in the urine was found to have fallen to 1.43 gm. The details of the experiment were the same as above reported. Mr. Smith found the diet quite as unpalatable as did Mr. Sawyer. On the second day he records in his notes: "Felt well except for slight nausea after meals." The nausea persisted, but on the fifth day was less and did not return until the ninth day. Flatulency was noted on the third day with cramp-like pains and heaviness in the epigastrium, and on several of the days the stool was loose. Some loss of energy was manifest on this and the subsequent days, but it had disappeared by the seventh, when the record states, "No nausea, felt well," and on the eighth, "No nausea, appetite good." The ninth day of the experiment was a trying twenty-four hours; "considerable nausea all day, had great difficulty in eating my meals on account of the nausea and sense of fulness. Felt weak and in low spirits, some abdominal distress," but the symptoms improved the following morning (tenth day); "passed a good night and felt much better, nausea, however, was marked all through the forenoon." Twelve gm. salt were now added to the daily diet, and the following change in the record is interesting: "At lunch took salt for first time with great relish. All nausea and epigastric distress disappeared after lunch; in evening felt very decided increase in strength and energy." Eleventh day: "No nausea or distress of any kind, great improvement in tone, physical and mental." It is only fair to state that Mr. Smith was aware that within three days from the commencement of his taking salt the experiment would definitely end, whereas up to this point the duration of the experiment was indefinite. He himself felt that "hope long deferred maketh the heart sick," and was not positive that the improvement in his feelings was wholly due to the salt.

The urine was examined for the first ten days daily for albumin, sugar, acetone and diacetic acid, but all of these substances were absent. The color remained normal throughout. The examination of the urinary sediment revealed no abnormal elements. Table 4 contains the result of the analyses.

Considerable difficulty was experienced in drying the feces. They were, therefore, first extracted with petroleum ether, and this extract made up to 1,000 c.c. The fat and nitrogen were then determined in each separately and the results combined. Before extraction the weight of the feces was 113 gm.; after gross extraction, 51.62 gm. dried to constant weight. The total quantity of fat extracted from the feces was 80.30 gm., and, as the amount of fat ingested during the nine days was

TABLE 3.—SULPHUR METABOLISM IN EXPERIMENT ON SAWYER.

Day.	Total Sulphur.	Inorganic Sulphates.	Ethereal Sulphates.	Total Sulphates.	Neutral Sulphur.	Inorganic Sulphates.	Ethereal Sulphates.	Total Sulphates.	Neutral Sulphur.
	gm.	gm.	gm.	gm.	gm.	P.C.	P.C.	P.C.	P.C.
1	0.96	0.71	0.05	0.76	0.20	74.0	5.2	79.2	20.8
2	0.97	0.76	0.06	0.82	0.15	78.3	6.2	84.5	15.5
3	0.99	0.79	0.06	0.85	0.14	79.8	6.1	85.9	14.1
4	0.98	0.82	0.06	0.88	0.10	83.6	6.1	89.7	10.3
5	1.04	0.81	0.08	0.89	0.15	77.9	7.7	85.6	14.4
6	1.09	0.86	0.07	0.93	0.16	78.9	6.4	85.3	14.7
7	1.06	0.83	0.07	0.90	0.16	78.3	6.6	84.9	15.1
8	1.17	0.90	0.10	1.00	0.17	76.9	8.6	85.5	15.5
9	1.15	0.90	0.05	0.95	0.20	78.3	4.3	82.6	17.4
10	1.12	0.88	0.08	0.96	0.16	78.6	7.1	85.7	14.3
11	1.01	0.80	0.05	0.85	0.16	79.2	5.0	84.2	15.8
12	1.08	0.85	0.07	0.92	0.16	78.7	6.5	85.2	14.8
13	1.10	0.86	0.07	0.93	0.17	78.2	6.3	84.5	15.5

1,080 gm., the quantity of fat absorbed was 92 per cent. The nitrogen in the dried feces amounted to 2.992 gm. If the nitrogen in the diet is reckoned as 103.5 gm., the absorption of nitrogen was 97 per cent.

It was intended to allow but 1,500 c.c. of water daily, but thirst became so troublesome that this quantity was increased on the first day and permanently changed to 2,000 c.c. from the fifth day on. It is interesting to note that the quantity of urine was only slightly greater than in the experiment with Sawyer or in Taylor's experiment. The average daily quantity of urine in Taylor's experiment was 1,172 c.c., in Sawyer's 1,240 c.c., and in Smith's 1,445 c.c.

The chlorin was but 1.43 gm. on the first day, due, as has been said, to the partial salt-free diet for the previous four days. It then decreased with slight variations until on the ninth day the total quantity of chlorin

was 0.17 gm., the limit reached in the experiment with Sawyer, and 0.2 gm. lower than that attained by Taylor. No sign of acetone or diacetic acid appearing, 12 gm. of salt (7.11 gm. chlorin) were added to the diet. It will be seen that nearly the whole of this quantity was retained in the body, for on the following day only 1.6 gm. were eliminated, and even on the next day only 2.26 gm. chlorin, but during the third day of the administration of salt the chlorin excreted showed a decided increase, and presumably an equilibrium was soon obtained. Neither on these three nor during the following days was a polyuria, as in Sawyer's case, observed. Thirty-one per cent., or 12.83 gm. chlorin, was retained in these three days.

TABLE 4.—INTAKE OF WATER, WEIGHT, URINARY ANALYSIS IN EXPERIMENT ON SMITH.

Day.	H_2O	Urine	Total N^2	NH^3	Ammonia—N	P_2O_5	Sp. Gr.	Cl.	Weight
	c.c.	c.c.	gm.	gm.	P.C.	gm.		gm.	kg.
1	1820	1810	10.9	.58	4.4	2.08	1009	1.43	*55.5
..	....	....	...	...	..	...	....	...	54.8
2	1500	1400	11.1	.61	4.5	1.09	1009	1.11	54.3
3	1500	1190	9.8	.64	5.4	.85	1010	.65	54.1
4	1500	1340	9.7	.80	6.6	.85	1008	.49	53.6
5	2000	1250	8.4	.75	7.3	.81	1008	.46	53.3
6	2000	1730	10.4	.98	8.2	.89	1007	.63	53.1
7	2000	1360	9.8	.94	7.9	.80	1008	.25	53.1
8	2000	1540	9.9	.94	7.9	.74	1007	.28	52.7
9	2000	1400	9.9	.96	7.9	.72	1009	.17	52.4
		ADDITION OF 12 GRAMS NACL TO DAILY DIET.							
10	2000	670	10.1	1.08	8.8	.42	1018	1.06	53.2
11	2000	510	9.6	1.21	10.3	.50	1026	2.26	54.2
12	2000	980	11.2	1.32	9.7	.88	1018	4.64	54.6

*Weight at commencement of experiment; other weights are those obtained at close of each subsequent twenty-four hours.

The loss of weight was less than in Sawyer's case. The reason is evident, because in the few days preceding the experiment the salt in the diet had been restricted, and during this period the weight fell about 1 kg. On the morning of the tenth day the weight was 52.4 kg. Coincident with the administration of salt this rose in the following seventy-two hours 2.2 kg. Corresponding to this increase in weight was a retention of water by the body which is at once manifest by the diminution in the urine during this period.

The average quantity of nitrogen eliminated in the urine per day in Taylor's experiment was 10.04 gm., in Sawyer's 11.2 gm., and in Smith's experiment 9.99 gm. The closeness of the three results is of considerable interest because of the difference of weight of the three individuals, Dr. Taylor weighing 80 kg., Mr. Sawyer 80 kg., and Mr. Smith 55 kg. The case of the establishment of nitrogenous equilibrium on the same

diet for these different weights is, of course, well known, but ever striking. The absorption of protein in Smith's case, as in Sawyer's, was excellent. The addition of salt to the diet increased the elimination of nitrogen in the urine, despite its smaller volume, by 3 per cent., but this is a quantity too small to be of significance. This observation corresponds to the more recent views on the action of salt on nitrogenous metabolism.

TABLE 5.—METABOLISM IN EXPERIMENT ON DIABETIC PATIENT.

Day.	Vol.	N.	NH_3	Urine Total Sugar.	Total Carb.	$NaHCO_3$	Carb. Bal.	Cl.
	c.c.	gm.	gm.	gm.	gm.	gm.	gm.	
1	1200	...	1.4	34.	96	16	+62	...
4	3000	..	2.8	66.	134	16	+58	...
5	4440	...	3.6	142.	158	16	+16	...
9	4900	..	3.4	..	91	32	..	...
11	4740	23.	1.2	119.	70	24	—49	2.0
12	5520	...	..	166.	83	20	—83	...
13	3930	25.	1.4	157.	73	16	—84	...
14	3180	.	1.1	102.	48	16	—54	...
15	3330	27.	2.3	107.	38	16	—69	1.03
16	3510	..	2.4	133.	38	16	—95	...
17	3120	23.6	2.7	119.	35	16	—84	0.38
18	3180	22.	3.2	102.	30	20	72	0.39
19	2400	17.	2.4	72.	50	20	—22	0.79
20	5280	.	3.3	116.	20	20	—96	2.56
21	2100	10.8	1.9	63.	44		—19	1.53
22	5910	25.8	3.7	100.	52		—48	7.93
23	5280	23.5	4.1	106.	17	8	—89	3.84
24	2400	17.3	3.1	77.	38	16	—39	3.48
27	2700	17.6	0.6	76.	50	12	—26	5.25
30	3360	..	2.3	54.	40	8	—14	..
62	1560	...	..	0.	69	0	+69	.

The absolute amount of ammonia rose slightly as the experiment advanced, but for this we have already given a partial explanation. On the twelfth day of the experiment (following the addition of 12 gm. of salt to the diet for three successive days) the amount of ammonia was greater than the quantity of ammonia obtained by Taylor on the last day of his experiment. Any lingering doubt as to the slight increase in ammonia obtained by Taylor on the last day of his experiment being dependent on the diminution of chlorin in the diet was thus dispelled.

While we were engaged in this work a patient with diabetes came under our observation, whose diet by chance contained an extremely small amount of salt. The case presented at first a mild form of diabetes with diffuse nephritis, but during a febrile attack the positive carbohydrate balance of 60 gm. changed to a minus carbohydrate balance of the most intense type. On the thirteenth day of observation the quantity of sugar in the urine was 157 gm., while the diet contained only 75 gm.

carbohydrates, thus giving a minus carbohydrate balance of 82 gm. This is about the maximum quantity of carbohydrates which could be formed out of the protein metabolized on this day, which was 25 gm. nitrogen (× 6¼) 156 gm. From this quantity of albumin it is customary to consider that (156 x 60) 94 gm. carbohydrate can be formed. Despite the severity of the case, the acidosis was only moderate, and on this day there was but 1.4 gm. ammonia.[6]

It is true that 16 gm. of sodium bicarbonate were administered in the twenty-four hours, but, as is well known, such a quantity will lower the ammonia only about 20 per cent. On the eleventh day of observation the chlorin in the urine was 2 gm.; on the fifteenth day, 1.03 gm.; on the seventeenth day, 0.38 gm., and on the eighteenth day, 0.39 gm. On the following day it began to rise as the low chlorin was discovered and salt was added to the diet. The observations made on this patient do not favor the view that a small quantity of salt in the diet of a diabetic patient increases the tendency to acidosis, because the general condition of the patient was better on the days with low chlorin excretion than in either the preceding or following periods, and the actual acidosis as measured by the excretion of ammonia was not notably affected. We would not attach too much significance, however, to this observation, because the excretion of chlorin may be variable even in the presence of a mild nephritis. The data of the case are recorded in Table 5. It is of interest that on the sixty-second day there was again a positive carbohydrate balance of 69 gm.

CONCLUSIONS.

The results of our experiments on two individuals placed on an ash-free diet for periods of thirteen and nine days, respectively, show no marked changes in metabolism. They simply represent the withdrawal of accessory salts from the body. They confirm the views of earlier writers, that it is practically impossible to diminish the chlorin of the body by more than 10 to 14 per cent., and that the loss of water is proportionate to this. No remarkable symptoms appeared, and those that

6. Such a severe case of diabetes with so slight an acidosis suggests a pancreatic origin as described by Brügsch (Therap. d. Gegenw., 1906, p. 337) and Hirschfeld (Berl. klin Wchnschr., 1905, xlii, 1609). No support for this opinion is furnished by the analysis of the feces which was made for me by Dr. F. B. Talbot: Total feces, 360 gm.; total dried feces, 20.758 gm. Percentage nitrogen, 4.2 per cent.; neutral fat, 1.9 per cent.; fatty acid, 3.9 per cent.; soap, 5.2 per cent.; total fat, 11 per cent. Total nitrogen in feces, 0.871 gm. Total fat in feces, 2.283 gm.

occurred were rather less than would be expected from such a diet, even though it contained a normal quantity of salts. We do not feel that they afford a basis for any far-reaching deductions as to changes in metabolism, and they certainly give no support to the view that the withdrawal of salts from the diet will cause an acidosis of the acetone variety. Clinical observations on the effect of the diminution of salt in a severe case of diabetes are in harmony with our experiments.

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THE INHIBITION OF PANCREATIC ACTIVITY BY EXTRACTS OF SUPRARENAL AND PITUITARY BODIES.*

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In a recent publication[1] we had the privilege of considering at some length the question of the activation of the pancreas by secretin, with especial reference to malnutrition and diabetes.

In it we pointed out, among other things, that in some animals, especially those which are carnivorous and are not provided with grinding molar teeth, in which animals there must, therefore, be either a large amount of acid gastric secretion or a high degree of acidity within the stomach, there was evidence that pro-secretin is present in the intestines in quantities larger than are found in human beings. We also reached the conclusion that the evidence to date for the absence or deficiency of pro-secretin as the cause of some cases of diabetes and malnutrition was insufficient.

These were our main findings as far as the present communication is concerned, but the experience gained in these connections led us to experiment further. The question of the relation of the pancreas and its evident activity, when excited by secretin, to digestion in general and to other organs in particular, is a very wide one, and, as we ventured to point out, offers a most promising and relatively unexplored field for research. It occurred to us that with a definite and sure method of activating at least the "external" secretion of that gland, and with an experience equal to measuring and interpreting its response, we had at hand a means whereby its correlation with other organs might be studied.

In his Harvey address[2] Starling says: "Secretin may be taken as a type of a whole group of chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect

*From the Pepper Laboratory of Clinical Medicine, and the Laboratory of Experimental Surgery, University of Pennsylvania; reported before the Society of Normal and Pathological Physiology, University of Pennsylvania, March 30, 1908.

1. Sweet, J. E. and Pemberton, R.: The Archives Int. Med., 1908, i, 231.
2. Starling, E. H.: Jour. Am. Med. Assn., March 14, 1908, l, 835.

correlation between the activities of the organs of origin and the organs in which they exert their specific effect." This effect, he says, as a deduction from many observations in this connection, is not due necessarily to the formation of a special substance which shall exert a specific influence on some distant organ, but possibly to the development in that distant organ of a specific sensibility to the common product of the first organ. The chemical adaptations which Starling considers and of which we know most, have resulted almost exclusively in increasing the activity of the responding organ. "We can not, however, draw sharp lines between the reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since, under physiologic circumstances, the latter is always an immediate consequence or accompaniment of the former."

Some unknown function of the pancreas by virtue of which it seems to have a close relation with diabetes has long been recognized, chiefly from von Mering and Minkowski's well-known observation, that extirpation of the pancreas causes glycosuria. As is well known, many agents may cause glycosuria when injected intravenously or otherwise given; for example, isotonic salt solution injected intravenously in large amounts; interference with the supply of oxygen; etherization; and, lastly and more specifically, adrenalin injected subcutaneously. Whatever the mechanism by which these agents act the last one named does so by producing a true hyperglycemia. Now the fact, on the one hand, that a small excess of suprarenal substance in the circulation of an animal, its own suprarenal glands being intact, produces glycosuria, and, on the other hand, that extirpation of the pancreas produces a like result, suggests an antagonism or balance of action between these two organs in particular which might profitably bear investigation. A relation of this kind has been suspected, though full experimental evidence has been lacking to establish it. Thus, Herter has shown that painting the pancreas with adrenalin causes glycosuria, but whether this is merely a feature of its action when injected subcutaneously or intravenously is not yet known. G. Zuelser[3] has advanced some ideas as to the interrelation of the adrenals and the pancreas. To quote his own words, he makes "the assumption that the secretion of the suprarenals is normally neutralized by the pancreas and that, therefore, the 'pancreatic diabetes' of Minkowski, which follows extirpation of the pancreas, is really a suprarenal diabetes." He also claims that by injecting simultaneously

3. Zuelser, G.: Berl. klin. Wchnschr., 1907, xliv, 474.

suprarenal extract and pancreatic juice, no glycosuria results. Pflüger[4] has shown that extirpation of the duodenum in frogs causes glycosuria. (It is from the duodenum, of course, that the pancreas normally obtains the stimulus for the discharge of its external secretion at least.) Ehrman[5] has found that this extirpation does not cause glycosuria in dogs; but Pflüger criticizes Ehrman's work on the ground that the separation of the pancreas from the intestines was not complete and that the animals did not survive the operation for a period long enough to make the experiments conclusive.

It was, therefore, with the basal thoughts just suggested that we sought to investigate the influence of various factors on the one gland of the body whose excitation by "hormones" can be induced at will, as a basis for inquiring into that further interdependence of organs which we know exists. Our first thought was to look within the body for factors which might have some effect, though the question of outside influences, such as "drugs," is an important one of itself.

We attempted, therefore, at the start, to influence in dogs the flow of pancreatic juice when excited by secretin, with intravenous injections of adrenalin chlorid, taking 3 c.c. at a dose.[6] Three c.c. of adrenalin was sufficient instantly and markedly to increase the blood pressure, without evidently injuring the animal during the period of observation and in a few minutes the blood pressure fell again to normal, so that the dose could be several times repeated.

We found on injecting adrenalin chlorid that the flow of pancreatic juice was almost at once inhibited and in most cases absolutely so. With injection of fair amounts it was at all times slowed, proportionately to the size of the dog and the activity of his pancreas. Moreover, the simultaneous injection of secretin and adrenalin resulted in a total absence of flow; and, furthermore, the injection of adrenalin a few moments prior to the injection of secretin prevented a flow. Occasionally, if the gland were very active and the dose of adrenalin moderate, a slight response to

4. Pflüger: Arch. f. d. ges. Physiol., 1907, cxix, 227.

5. Ehrman: Arch. f. d. ges. Physiol., 1907, cxix, 295.

6. The secretin we used was prepared from normal dog intestines. The animals on which we experimented were all dogs. They were kept under profound ether anesthesia, and, at the end of the experiment, were killed. The amounts of secretin injected were 10 c.c. of solutions made from 300 to 400 c.c. 0.4 per cent. HCl. This quantity of acid was found well adapted to the extraction of mucosa from the upper four feet of dog intestines, and served for numerous observations, making a total of about 150 to 200 c.c. of secretin solution. The details of preparation are otherwise as given in our previous article (THE ARCHIVES INT. MED., 1908, i, 231).

flow would occur late, as though, in the end, the action of the secretory factor had preponderated.

In considering the matter, one of our first thoughts was, of course, that the inhibitory power of adrenalin was due to its blood-pressure-raising principle, notwithstanding the fact that changes in blood pressure are well known to have little influence in the output of most glands, and that the pressure in the secretory duct of such glands may, without much effect, be higher or lower than that in the vessels supplying it. This is well illustrated by numerous long-established experiments on the salivary glands. As a matter of fact, however, the injection of secretin is followed by an immediate and pronounced fall in the blood pressure. The blood-pressure-lowering element of secretin is probably purely incidental, as shown by Bayliss and Starling, and, as can be seen from our records, is a feature of many extracts of tissue because of various elements present. Further, under some circumstances, after the injection of adrenalin of known vasomotor activity, the blood pressure has for various reasons failed to rise very much, and again, after adrenalin injections, secretin has greatly reduced the blood pressure to a point much below normal, and yet no flow has resulted in either event, showing conclusively that this action is not the result of high blood pressure. Further, the simultaneous injection of both agents frequently results in such an antagonism of the elements which affect the blood pressure that no change in its level occurs and still no flow appears. We shall later refer fully, after considering further experiments, to some results obtained with old solutions of adrenalin which had undergone changes whereby they lost their property of preventing pancreatic flow, but yet powerfully raised the blood pressure. A flow, therefore, took place with the blood pressure raised almost to a maximum by adrenalin. More direct experiments to this end can be conducted with difficulty, as no other known substance raises the blood pressure to a degree at all comparable with adrenalin.

That this inhibition of secretion is not a feature of any general action of adrenalin is shown by a number of observations, the results of which are summarized as follows by Cushny:[7] "The secretion of the salivary gland and of the mucous glands of the mouth and throat is increased, apparently through stimulation of the nerve terminations, as under pilocarpin. The secretion is arrested by atropin, but can be reinstated by larger amounts of suprarenal extract, which is a more powerful antagonist to atropin than pilocarpin. The lacrimal gland and the bile

7. Cushing, Arthur R.: Pharmacology and Therapeutics, Lea Brothers & Co., Philadelphia.

are also increased." Speaking of the blood pressure, he says: "This active principle exists only in the medulla of the gland and, therefore, does not represent the whole function of the organ, in all probability."

It may be well here to mention the methods by which we recorded the observations which appear later. In our previous work we measured pancreatic activity by registering with a watch the exact moment at which the flow of juice through the canula in the duct of Wirsung passed definite graduations marked along the canula. This method was accurate enough, but not at all graphic and was, as well, voluminous in reproduction, so we had recourse to the following method:

The blood pressure was recorded on a kymographic drum by means of a manometer in the femoral or carotid artery, and the respiration by a manometer introduced into the trachea. By means of the electric push-button connected with the pen drawing the base line on the drum, it was possible, by watching the flow of juice through a graduated canula placed in the duct as usual, to record in vertical and momentary elevations of the base line the exact moments at which the juice flowed past any given division.

In order that the record of an experiment, which often covered a period of several hours, might be made continuous, we made use of a modification of the well-known "endless roll," a method which had for our purpose the advantages of recording the blood pressure in all its variations from the normal established at the beginning of the experiment.[8]

The experiments above recorded of the action of adrenalin were repeated a great many times and, as our tracings show, with almost invariably the same results. The amount generally used was 3 c.c. of the "adrenalin chlorid" of Parke, Davis & Co., which is said to contain two and one-quarter grains of chloretone to the ounce. In order to obviate the possibility of the latter preservative being a factor we prepared several chloretone solutions of different strengths, one of over twice the strength in which it occurs in adrenalin, but no inhibitory effect could be observed from it. We next made up a solution of pure adrenalin from the dried active extract of the suprarenal glands also on the market. This is said to contain no preservative of any sort, but a solution made from it of the same strength as that containing chloretone again gave the same results. Finally, we made a suprarenal extract of our own, from the suprarenal glands of thirteen dogs on which various surgical

8. We are under great obligations to Prof. E. T. Reichert for his kindness in devising the simple and effective kymograph which proved so perfect for the use of the endless paper roll. We are further indebted to him for assistance in many technical points.

operations had been performed some weeks previously in the course of experimental surgery at the University of Pennsylvania. These animals were in good health and were all killed by gas at the same time for autopsy study; advantage was taken of this fact to obtain the suprarenals. The glands were run through a hash machine and the resulting mass ground up with sand and about 30 c.c. of normal salt solution in a mortar for about fifteen minutes till the whole was reduced to a uniform pulp. Salt solution was then added to a total of 78 c.c. and the mortar contents strained through unbleached muslin. This preparation was opaque, white and cloudy in appearance, and our observations show that to all intents and purposes it had all the properties of that put on the market in regard to both blood pressure and inhibition of pancreatic flow. On an earlier occasion we made a normal salt solution extract from the two suprarenals of one dog and added to it 1 c.c. of a saturated solution of chloretone. This preparation was also active in all respects.

In order to establish any peculiarity or specificity of action in this connection, however, it was then necessary to utilize other glandular extracts and other substances in the same connection.

To this end we experimented with as many animal extracts of known activity as could be obtained. There are, of course, but few such, and there is only one of any definite therapeutic value, viz., the thyroid. A tablet of dried thyroid extract (the therapeutic dose for an adult human being) was ground up in a mortar and the powder rubbed up with 10 c.c. of water. The liquid assumed a brownish color, indicating some solubility of the substance, but for the greater part this injection consisted of a fine suspension. A solution of thyroid extract was also made by treating the mashed and ground pulp of two sheep thyroids with slightly more glycerin than was sufficient to cover them. This was allowed to extract all night and then diluted one-half with water, strained and used in various amounts for injection. There can be no question that this preparation contained much of the peculiar colloid thyroid elaboration, because the slightest amount gave the characteristic viscid reaction which occurs when the latter is treated with alkali. The glands used in this instance were taken from fresh material obtained from the abattoir and used at the University Hospital in the treatment of a case of myxedema which was improving rapidly. We also tried a liquid preparation of thyroid extract distributed by the manufacturers. All of the above thyroid extracts, however, were without influence on the flow of juice.

It has been shown by Schäffer and Oliver and others that the pituitary gland contains a substance which acts somewhat analogously to the active principle of the suprarenals, in that it raises blood pressure. It does this to a degree less than the latter, though the effect is said to be

continued somewhat longer. We attempted next, therefore, to obtain an extract of the pituitary body, and used first a liquid preparation said to be of the infundibular portion, distributed by Parke, Davis & Co. for experimental clinical observation. In answer to some questions addressed to them by letter, the manufacturers of this solution state that it contains 0.5 per cent. of chloretone. Taking the same dose of this that we used of adrenalin chlorid, we injected it after exciting the flow by secretin and obtained almost the same consequences as followed the use of adrenalin. In other words, the pancreatic flow was at once cut short and generally completely inhibited. In nearly every instance the rise in blood pressure was considerably less than is witnessed after the same dose of adrenalin, and, moreover, it was less abrupt, though the longer continuance noted by some observers was not so apparent. Notwithstanding its evidently inferior activity in respect to blood pressure, its inhibitory action on pancreatic juice seemed to be more marked. The cessation was in most cases more prompt, and on several occasions a second injection of secretin failed to excite a response after an interval of time following the injection of pituitary extract such as would probably have insured a flow, even though slight, had adrenalin been used, showing apparently that this preventive action sometimes lasts longer in the case of the pituitary gland. That this feature in no way depends on an increase in blood pressure is better illustrated by the pituitary than by the fresh adrenal extracts, since the former on many occasions fails to raise the blood pressure and more frequently the rise is so slight and so temporary as to be of evidently little consequence. In this respect of raising the blood pressure, the pituitary extracts used by us were by no means as constant or reliable as those made from the suprarenals.

On varying the time of injection, as we had done with adrenalin, and giving the extract after excitation of the pancreas by secretin, then before its excitation, and, finally, with the injection of secretin, we met with nearly identical results. In both of the latter instances the flow is prevented by the dose mentioned (3 c.c.), and in the former it is greatly slowed and generally promptly stopped. In regard to both the adrenal and pituitary extracts it is noticeable that their action is apparently more marked when the injections precede or are coincident with the injection of secretin than when they follow it. Sometimes, with a very active pancreas, the initial dose of adrenal or pituitary would be insufficient to retard very much a violent response to secretin, but we found that if given before the injection of secretin the flow was always inhibited.

The commercial extract of pituitary gland which we first tried (the exact nature of which was, of course, entirely unknown to us) was open

to the same theoretical objection as adrenalin, and it was possible that methods of preparation or the preservatives used in its manufacture might conceivably produce these effects or modify in some way its own properties; indeed, they might actually disguise those with which we were concerned. We, therefore, determined to prepare our own extract, which we did as follows:

On the occasion mentioned above, when thirteen dogs were killed, we removed separately both portions of the pituitary gland, nervous and glandular. This procedure is relatively simple in the dog, as the organ is easy of access and is exposed to view as soon as the frontal lobes of the brain are raised. The nervous part in the dog is a small white globule about the size of a grape-seed, and on being crushed extrudes a slightly viscid juice which can be rubbed into a paste. To the thirteen infundibular portions so treated we added 30 c.c. of normal salt solution, agitating the whole for some time to insure as complete extraction or solution as possible. The resulting fluid contained very little residue of any sort and was transferred directly to a small sterile Erlenmeyer flask. The glandular portion of the pituitary was then treated in the same way with an equal amount of salt solution and transferred to another flask. It might be mentioned here that, while histologically the glandular portion of the pituitary body is epithelial tissue, it in no way resembled a gland macroscopically, and by the uninitiated eye would be taken for the nervous element. On being crushed it resembles so much fairly dense tissue and gives a solution more tinged with blood than the nervous extract, which is almost white in color.

The extract from the nervous portion of the pituitary was active in regard both to blood pressure and to the suppression of the pancreatic flow, agreeing in all respects with the other preparations tried. The dose used was 10 c.c. of extract, which was equivalent to the nervous fraction of about four and one-third whole glands. The blood pressure was raised to a degree somewhat less than was seen after most of the other pituitary injections, but this may well be accounted for by the strength of the preparation, which must have been considerably lower in actual extractive content than the commercial article, which is made from the organs of larger animals.

The extract from the epithelial portion of the pituitary was injected without any evident effect on either the blood pressure or the flow of juice, which is quite remarkable, considering the immediate contiguity of the structures, and argues much for a specificity of action. We shall have more to say on this subject later.

Having satisfied ourselves that the pituitary and the suprarenal both contain something whose action on the pancreatic flow is marked, it remained now to investigate other tissues. The one of known physiologic interest as regards its therapeutic action we had already tried with a negative result, but it could not be postulated that other organs or other tissues might not contain some principle which would act analogously. Consequently we made extracts of the parenchyma of other glands and of other nervous tissue. Of the former the epithelial portion of the pituitary already served as a striking instance. About one-fourth of the liver of a freshly killed dog was put through a hash machine and then ground with sand and a small amount of normal salt solution in a mortar until a fairly uniform mass resulted. More normal salt solution was then added, making a total of 150 c.c. used, and the whole agitated and ground in a mortar as well as possible for about twenty minutes. It was then passed through unbleached muslin to free it from sand and tissue residue and then transferred to a sterile Erlenmeyer flask.

In addition to the above, on another occasion, a glycerin extract of liver was made by adding about 150 c.c. of glycerin to the mass passed through the hash machine as recorded, and after agitation and pressure in a mortar the whole was allowed to extract for twenty-four hours. A small amount of water was then added and the mass strained. Another watery extract had been previously prepared and this procedure was repeated only because it was thought that an unavoidable delay of some hours might in some way have impaired the activity of the first. With the exception just noted, the glandular extracts of our own preparation on which we based conclusions were all made within a few hours of the death of the dogs and injected within a few hours at latest after their preparation.[9] None of the liver preparations seemed, however, to have the slightest effect on the flow of juice, though the blood pressure was sometimes considerably lowered, as has been shown by Halliburton, Dixon and others to be the case with several organ extracts.

We next experimented with nervous tissue, for which purpose we obtained the brain of a freshly-killed dog, passed it entire through a hash machine and then ground the pulp in a mortar with sand and a total of about 130 c.c. aqua distillata. Distilled water was used inadvertently instead of normal salt solution, as in the other experiments.

While the subject of the depressing effect of extracts of nervous tissue has already been pretty thoroughly studied by Halliburton and others, it

9. The animals were killed between 6 and 7 a. m. The suprarenal and pituitary glands removed between 8 and 10 a. m., and extracts made by noon. They were injected during the afternoon and evening of the same day.

is interesting, apart from their relation to pancreatic activity, to compare the systemic effects produced by injections of this last preparation with those of other extracts. The amount of fresh liver substance taken for extractive purposes was about one-quarter of the organ, to which was added 150 c.c. of extracting fluid. The brain of a medium-sized dog compares closely with this in bulk as well as in percentage of water. We macerated the brain with 110 c.c. of extracting fluid, so that bulk for bulk the solutions were approximately equal, putting aside the question of their respective yields on attempts at extraction. The first dose of brain extract used was 10 c.c. and with a slight fluttering and preliminary rise of blood pressure the dog almost instantly died. The doses of liver and other tissue extracts were 10 c.c. and more. The next dose of brain extract was 5 c.c., and with a marked fall of blood pressure this animal died at once, though nothing had been previously injected into him. The next dose administered was 1 c.c. of extract in 10 c.c. H_2O, and again a fresh animal at once died; and finally we injected 0.25 c.c. diluted with 10 c.c. of water, and though the blood pressure fell alarmingly and it seemed by the cardiac inhibition and small excursion of pulse that this animal would also succumb, the blood pressure rose again and the animal seemed to recover. However, after one or two injections of secretin and adrenalin, which had been well borne in nearly every other instance, this dog also suddenly died, apparently from injury due to the first injection.

It is interesting to note that, notwithstanding the powerful and almost lethal effect of even a small dose of the watery extract of brain tissue, absolutely no effect could be detected on the flow of pancreatic juice, which continued, as we had frequently observed before, when the animal was moribund.

That the inhibitory action of the pituitary is therefore not a function of nervous tissue in general is clearly seen, because the mass of the brain as compared with that of the diminutive pituitary bodies is very great, and the effect of its extract, if potent, should be both actually and relatively greater. Moreover, the pituitary gland and brain substance are, of course, in the most intimate contact, and were this activity of the hypophysis common to other higher nervous tissue it is almost inconceivable that it should be so sharply differentiated in our work. Whether every part of the brain would act similarly in extract, or whether in such a gross method of extraction we have diluted, beyond evident potency, tissues from other active regions, is problematic.

In view of the relation which the pituitary is supposed to bear to the testes, as evidenced by those cases of acromegaly in which a lesion is dem-

onstrable in the hypophysis, and testicles also, it seemed advisable to try the effect of extracts from testicular tissues, although the immediate physiologic effect of these on the circulation and economy in general has been extensively studied by Dixon. We macerated two dog testes freed of their epididymes and then ground them up as before, with sand and mortar, finally adding a total of 78 c.c. of normal salt solution. The whole was then meshed through linen and injected in the usual manner, but no effect on the flow of juice was noticeable, whatever the time of the injections.

Our purpose in making glandular extracts of our own was two-fold. In the first place, such a procedure was necessary to give us the material we needed to widen the scope of our work; and, in the second place, it seemed advisable to test whether, by the methods we used, we could extract the features of certain glands which are known to be present in them. Failing in that, it could hardly be assumed that we were capable of extracting the active features of other parts; but if, on the other hand, we were successful, it could be reasonably believed that in the tissues under consideration no active substance was present, or that, if present, it was not susceptible of extraction by these methods. We desire to be understood, therefore, as claiming, not that this observed antagonism of action is one positively peculiar to two organs alone, but that it is one manifested by them under certain conditions of treatment and a property which we have been unable to extend as yet to other tissues. That a certain degree of specificity is probable from the evidence now at hand must be granted. Whether further observation will corroborate or disprove this it remains for the future to show.

We also experimented with atropin. According to the physiologists, atropin depresses or suppresses practically every secretory activity in the body except that of the kidney, and possibly the pancreas. On the flow of pancreatic juice, however, we were unable to perceive the slightest effect from it. The amounts administered were nearer the physiologic limit for a dog than were the doses of adrenalin, which can be repeatedly given in quantities of 10 c.c. at a time, in the form of the commercial adrenalin chlorid, without much evident injury. Our records show that one of our dogs received 1/300 gr. atropin sulphate, followed in a few minutes by another dose of 1/300 gr., without evident result on the flow, whereas another fresh dog died from what resembled paralysis of the respiratory center, apparently as the immediate result of an injection of 1/150 gr. Atropin neither prevented nor stopped the flow of juice.

Efforts were also made to simulate with digitalis the rise in blood pressure produced by adrenalin and pituitary extract, but no effect of any value could be obtained in this connection.

Now it is true that to speak of making an extract of so highly organized and differentiated a structure as the liver, not to mention the brain, seems crude; but it is also true that in considering such a problem as we have here we must first begin with the lowest terms and with such methods as are compatible with our knowledge of the subject. Having found in two organs some active substance which can be extracted by their treatment with salt solution, we are driven to applying the same methods to other parts of the economy if we would learn more of its extent and distribution. It can well be urged that in different sites the same property or different properties require different methods of extraction, and that treatment with water or glycerin in one instance will not effect the same result in another. Nevertheless, we have indubitable proof that both water and glycerin can extract certain of their activities from several organs, as, for example, the suprarenal and thyroid glands respectively, and we also have equal proof that from other regions of the body can be derived substances of such toxicity that an animal subjected to their action immediately succumbs. Just which of their numerous ingredients are responsible for these properties we are often unable accurately to say, and it is even a disputed point as to what factor in the extraction of nervous tissue produces the profound depression of the vascular system which is followed by death. That the same methods of attack, under such circumstances, should therefore necessarily appear superficial and crude follows perforce. When we consider how easy of extraction by almost identical means is that principle of the adrenals with which we are most familiar, namely, the blood-pressure-raising element, it seems astounding that its discovery should date from a period so recent as 1894; and if it be borne in mind that such methods in that instance furnished striking knowledge and that we have progressed little since then in our knowledge of the functions of the suprarenals themselves, the methods necessary in dealing with such an unknown subject appear less general and more definitely specific.

We hope to be able to investigate this antagonism of action, after separating the pancreas from its nerve supply, as thoroughly as possible, since it may well be that the effects noted result from the mediation of the sympathetic system. It is of some interest to consider here briefly a few points in the morphology of the suprarenals and the pituitary in their relation to our observations. It has been shown[2, 7, 10] that the

10. Dixon: Jour. Physiol., Cambridge, 1900-1901, xxvi.

classic effects of adrenalin are produced in large part by its action on the sympathetics, and wherever we test its action, in respects other than those under consideration, we find the results identical with those obtained by stimulation of this system of nerves and ganglia. The suprarenals are derived morphologically from two sources, the cortex coming from the mesoblastic tissue and the medulla from a direct outgrowth of the sympathetic system. As evidence of the latter we find in many of the lower orders distinct nervous tissues consisting of neurogliar cells, which are, however, harder to differentiate in man; indeed, in certain forms, viz., teleostean fishes,[2] the two parts, medulla and cortex, remain separate through life. Now, an interesting corollary to our observed analogy of action between the suprarenals and the pituitary is the fact that morphologically we could reasonably conceive of these two organs as having something in common. The pituitary body, like the suprarenals, consists of two parts, and again like the adrenals, each part has a separate derivation. The anterior lobe has its origin from one of the branchial clefts in a pouch of buccal mucous membrane.[11] The posterior is derived, like the medulla of the adrenal, from the ectoderm. It comes from the floor of the third ventricle, to which it remains attached by a stalk, viz., the infundibulum. According to some, the larger anterior lobe has two sources, the primitive oral tissue in early life and the anterior portion of the alimentary canal.[12] Wiederscheim[13] says that "the secretion from the pituitary gland formerly passed into the ventricles, and one of the more recent theories assumes that the pituitary corresponds to the primitive mouth (palæostoma) of the proto-vertebrata, which to a greater or less extent is represented by the combined impaired nasal and pituitary passage of cyclostomes." In certain mammals there can yet be seen evidences of the passage which connected the anterior part with the posterior part and thence with the third ventricle.[11] These facts by themselves are of interest, and in connection with our observations they are not in discord. That an organ so anatomically remote as the pituitary should have a definite influence on a gland in possible morphological relation to it is therefore less surprising.

As with the adrenals, it is that part derived from the nervous system which gives rise to the blood-pressure as well as the inhibitory element. For neither the epithelial portion of the pituitary nor the cortex of the suprarenals, however, is there any recognized function. The two parts

11. Herring: Jour. Physiol., Cambridge, xxxvi, No. 6.

12. Stengel: Text-Book of Pathology, Philadelphia, Saunders, 1906. Davidoff, Böhm: Text-Book of Histology, Huber, 1900, p. 380.

13. Wiederscheim: Comparative Anatomy of Vertebrates, Parker, 1897, p. 155

of the pituitary can be worked up and extracted separately, as noted above, but this has not yet been possible with the adrenal, so far as its inhibitory action is concerned, although from the suggestive analogies between these two organs and the very evident limitation of the inhibitory feature of the pituitary to its nervous moiety, it seems probable that the adrenalin inhibition has the same point of origin as the blood-pressure factor, viz., the medulla; still, this can not be postulated at present, and it may be, indeed, that we have here an expression of one of the functions of the suprarenal cortex.

Since the completion of our experiments some work has been reported by Botazzi, D'Errico and Jappeli,[14] in which they obtained an inhibition of flow from the salivary gland by painting it with adrenalin. Stimulation of the chorda tympani then failed to give a response. Without questioning the accuracy of their findings, which are at variance with the work quoted by Cushny, the question as they present it does not argue an inhibitory action on the salivary gland analogous to that observed by us on the pancreas. In the first place, they are dealing with a gland excited by purely nervous means and not by a chemical substance which reaches it through the blood. Again, and more important, the inhibited salivary gland is stated by the above Italian workers to be in the highest degree anemic after local application, a condition in which it is hard to conceive of its having an activity of any sort, since it is for the time being out of commission. This is, of course, in no way comparable to the action of adrenalin on the pancreas (if its action *is* on the pancreas) when the flow of juice in the latter organ is inhibited by a systemic injection into the jugular vein. And, furthermore, this view of the matter does not explain the action of the pituitary which has, as far as we know, no such reported action on glands. Finally, to ascribe to an ischemia of the pancreas the inhibition of pancreatic flow after jugular injection of a small dose of adrenalin, supposes that most or all of the organs of the body become anemic to such a degree that they can no longer act, which is stretching a hypothesis beyond the facts to support it.

It is somewhat immaterial, however, whether adrenalin acts on the pancreas alone or also on other organs, since the point of interest is that in affecting it at all in this way it affects the one gland of the body whose connection with diabetes is best established. That it might also affect certain other analogous structures with inhibition would not be surprising, though the evidence now is against it.

14. Botazzi, D'Errico and Jappeli: Physiol. Inst. Univ., Naples; Biochem. Ztschr., January, 1908, vii, 431.

One feature of our work demands some notice and is of suggestive interest. On the day when we experimented with the pituitary and suprarenal extracts of our own manufacture we made our first injections about 1 p. m. The preparations used for this purpose had been made between 10 a. m. and 12 m. from the animals killed early that morning as noted. The samples of suprarenal extract first injected were vigorously active. Because of press of work under the desire to utilize our preparations before they were affected by decomposition, we were unable to use the pituitary extracts before evening, about 8 p. m. Although tried then for the first time, about eight hours or more after their manufacture, they acted vigorously, as stated. On endeavoring to repeat with the suprarenal extracts our work with them of the early afternoon, however, we were able to get no inhibitory action, although the blood pressure was still raised. To control this conflicting observation we tried a preparation of adrenalin made some weeks previously from the dried extract of the suprarenal gland put on the market by Parke, Davis & Co. in small grain vials and said to be free from preservatives. This solution corresponded purposely, in adrenalin strength, to the usual commercial article containing the preservative chloretone. It was remarked by one of us immediately prior to the injection, while filling the syringe, that the solution showed a slight mould. It had been used many times before and had in every instance been powerfully and emphatically active, though there had been a lapse of perhaps a week since its last use. To our surprise, this preparation raised the blood pressure decidedly, but was absolutely without influence on the flow from the pancreas. We then tried an injection of the commercial adrenalin chlorid solution, also some weeks old but containing chloretone, which both raised the blood pressure and inhibited the flow, as we had repeatedly observed before.

The absolute significance of these observations can not be established until we repeat our experiments in this particular connection, but the most obvious and reasonable deduction is that the extracts from the suprarenal glands contain two or more substances, one of which acts on the blood pressure and one of which acts to inhibit the flow of juice. The former of these seems the more stable of the two and resists decomposition for a considerable time, but the latter loses its activity very shortly, perhaps in a few hours. In the instance of the preparations of our own manufacture, from dog organs, the tissues and the extracts from them were, of course, contaminated from the start with the ordinary postmortem putrefactive agents, and in order in no way to impair the efficiency of the extracts no attempt was made to introduce preservatives or sterilize them. The "dried extract" of the gland, however, was presumably

sterile to start with and the solution made from it remained fairly free from infection except in so far as it was contaminated by the initial weighing of the dry powder. Sterile salt solution was added to this and the solution kept on ice in a corked bottle, the only further contaminating agent, beyond contact with the air when the cork was removed, being the needle of the syringe. This was always thoroughly cleansed with water after each injection, though not sterilized. Under these circumstances decomposition would surely proceed rapidly from the start in the case of our dog preparations, but slowly in the case of the others. We can offer no explanation for the apparently greater stability of the pituitary inhibitory factor except that the pituitary glands, being small, were easily mashed in a small agate mortar and quickly transferred to small flasks, while the suprarenals required longer and more vigorous treatment with sand in a mortar, had also first been run through a hash machine, and were hence more open to infection.

The process which operated to destroy the activity of these preparations may be simply that of decomposition by putrefactive organisms, or it may be, on the other hand, of an oxidative nature more like that to which Bayliss and Starling have ascribed the slow deterioration of secretin and its more rapid loss of activity on evaporation in efforts to concentrate it. All the points here suggested are yet to be worked out, however, in their relation to our work.

We are by no means sure, at the present writing, of the full interpretation of the results under discussion. They are but the earliest steps in a line of work on which further observations may throw much light. They seem to us, however, to be very suggestive in their possible bearing on other interglandular relations, on the medium in which these are maintained, and possibly on a new conception of the interdependence of various organs now the subject of speculation. For these reasons it seemed advisable to publish our results at this stage and make their further amplification the subject of later contributions.

In studying the records, and indeed through a consideration of all our work, it must be borne in mind that we are dealing with a balance of power between various factors, no one of which is susceptible of exact definition or measurement. As with the study of the pharmacologic action of drugs, there must be taken into consideration, besides the size of the dose, the activity of the organ under consideration, and the condition and size of the animal as a whole. What may be quite sufficient markedly to affect one animal may be altogether inadequate in the treatment of another.

Popielski[15] has recently taken issue with Bayliss and Starling as to the method of action on the pancreas of acid extracts of the intestinal mucosa and indeed as to the existence of secretin at all, as a specific excitor. He also claims to be able to produce pancreatic activity with extracts of stomach and large intestine. The main point of discussion in this controversy is somewhat beside our present issue, though there are a number of incidental features which have a close relation to some observations of our own.

Popielski thinks that the secretion of pancreatic juice after excitation by secretin is dependent on a fall of blood pressure and that if the blood pressure be maintained high no flow results. He uses adrenalin to raise the blood pressure and notes with the high pressure that there is no flow. He concludes also, as an incidental point, that adrenalin, in itself, does not inhibit pancreatic activity. He considers that stimulation of the pancreas by secretin and stimulation by HCl in the duodenum are different processes. Now, it seems to us that our work throws some light on several of these questions. In the first place, we have obtained some further results with adrenalin (already mentioned and to be referred to again presently). Popielski's use of it seems to have been solely to raise the blood pressure. In so doing he has apparently overlooked the other feature of it, for, while he notes incidentally that it does stop the pancreatic flow, he thinks this phenomenon due to the high blood pressure and not to the adrenalin proper. He specifically states that adrenalin in itself does not influence the flow of juice. Now, as we mentioned above, one of our series of experiments conclusively proves that it is possible to obtain a flow after the injection of secretin, despite the fact that the blood pressure is raised to a high point. We refer to those observations, happened on by chance, in which exposure to air and apparent decomposition had destroyed the inhibitory factor of a solution of adrenalin, but allowed the blood pressure element still to act. Whatever the true explanation of this—and we offer nothing positive on this point—it is a fact that on several occasions such a solution distinctly raised the blood pressure sometimes to a very high point, and yet the juice flowed. To have noted this once would be sufficient to prove it possible. We have a number of such records. Not only does this prove that it is not the blood-pressure element alone of adrenalin which affects the flow of juice, but it also proves that, as just stated, a flow may take place following secretin when the pressure is high and that, therefore, a low blood pressure is *not*, as Popielski claims, a feature necessary to it.

15. Popielski: Arch. f. d. ges. Physiol., 1907, cxx, 451; 1908, cxxi, 239.

His findings in regard to the failure of atropin to affect the flow are in agreement with ours, viz., that no inhibition results from it. We have as yet been unable to effect a secretion from the pancreas by the injection of extracts of other tissues, though we have not yet tried those particular tissues (i. e., stomach and large intestine) used by Popielski. He states that a watery solution is sufficient to extract the exciting factor, and we used also water and normal salt solution in our work. We obtained no flow, but, on the contrary, from certain tissues, as mentioned above, we obtained an inhibition. We also made an acid extract of the pancreas with 0.4 per cent. HCl, and treated the whole exactly as we did a coincidently prepared and active solution of secretin. No flow resulted, however, from the acid extract of pancreas.

It should be mentioned also that after section of both vagi we still obtained the inhibitory effect from suprarenal and pituitary extracts.

Some further interesting observations have recently appeared which deserve reference. Fleig[16] reports on the physiologic properties and toxicity of normal pancreatic juice and that provoked artificially. He considers as normal, juice elaborated under the influence of chyme secreted through a duodenal fistula in an otherwise sound dog and then injected into the duodenum of the dog whose pancreas is under consideration. The quantities of chyme required under these circumstances are considerable (20 to 30 c.c.) and they must be repeatedly injected (every ten to twenty minutes) to induce a proper flow. The secretion thus provoked differs much from that which follows intraduodenal injections of 0.3 per cent. HCl, the time required is much greater and the quantity of juice furnished "infinitely less." Under the influence of chyme thus conducted the juice remains very thick and viscid from beginning to end, whereas juices secreted after more artificial stimulation differ in this and other physiologic respects until after repeated injections of secretin. For example, the pancreatic juice may have hardly any of its normal physical characters.

Natural and artificial secretions also vary in their toxicity when injected into animals, the former being more powerful in this respect. The lowered toxicity of secretin juices, Fleig thinks, is in consonance with their poor content of solids rather than their relative tryptic inactivity. He says that the above conditions are true also in general of the biliary and salivary secretions.

Now it seems to us that the above results are what might be expected. That a purely artificial and foreign substance, such as secretin, full of other extraneous matter and differing itself not only in quantity but in

16. Fleig: Compt. rend. Soc. de biol., May 8, 1905, No. 15.

quality from the normal pancreatic excitant, should produce the same juice as does the slow extruder gastric chyme, acting over perhaps many hours, seems unlikely in the highest degree. It would, indeed, be extraordinary if the results of such varied stimulation were the same. The amount of excitant which reaches the pancreas normally from the duodenum is surely a small or moderate quantity; that which is injected with secretin is not only concentrated in preparation from many feet of gut, but is injected in a few seconds to spend its whole force at once. It is hard to see how any gland could long continue to elaborate a normal product under such vigorous treatment. We hope to investigate shortly the effect of adrenalin and pituitary extracts on the pancreatic flow after stimuli other than secretin, especially chyme from a gastric fistula in an otherwise healthy dog, but it seems probable that the principles are much the same on which depends secretion after all of these and that the results of such work will be in harmony with what we have already seen. If adrenalin and pituitary extract inhibit the sudden and violent initial flow from secretin, it is conceivable that they would also affect the mild response from other stimuli. It must be remembered that the altered nature of pancreatic juice after secretin comes as the result of protracted and powerful stimulation and not from the initial dose.

It is interesting to note in connection with our work the observations of Meyer[17] and Frouin,[18] which afford some evidence that extirpation of the suprarenals, after the induction of diabetes in depancreated animals, modifies the severity of the diabetes and reduces the elimination of sugar.

We hope to concern ourselves now with the question of the site of this antagonism between the pituitary and suprarenal glands, on the one hand, and the pancreas, on the other; with the question of whether it is a chemical action, in the general sense of the word, which occurs in the circulation, or whether it is the result of some influence exerted on the pancreas alone; or whether, again, it is accomplished through a nervous mechanism. The solution of these problems should give information of value in studying the influence of such factors on the so-called "internal secretion" of the pancreas, and its relation to diabetes. Whether, on hypodermic injection, adrenalin produces glycosuria, which it does in a few minutes, by virtue of an inhibition of the internal secretion of the pancreas analogous to the inhibition of its external and visible discharge, is yet to be investigated. We have been unable to produce a glycosuria after either the subcutaneous or intravenous injection of 4 c.c. of pituitary extract. The solution used was made for us without

17. Meyer: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 219.
18. Frouin: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 216.

chlorctone by the manufacturers, but we have not as yet controlled its inhibitory activity on the external pancreatic flow and, therefore, can not be positive on this point.

It yet remains to investigate more thoroughly the degree of specificity by trying the effects of other tissues and other methods of extraction; but, whatever the result of this, it appears reasonably certain that this feature to which we have called attention is one peculiar to certain structures, and from the data now available the expression of hitherto unknown properties of several organs.

In conclusion, it is a pleasure and a duty to express our great obligation to Dr. David L. Edsall for his constant and helpful interest in the work, and we also wish to thank Dr. John Marshall for many courtesies in the loan and equipment of apparatus.

CONCLUSIONS.

1. The suprarenal glands and the nervous moiety of the pituitary body in dogs contain something which, on extraction with salt solution and intravenous injection into dogs, cuts short the flow of pancreatic juice, after the administration of secretin. It also prevents the stimulation of the gland by secretin if its injection precedes the secretin.

2. This feature has been found, to date, in no other tissues.

3. It is independent of the general rise in blood pressure seen after the intravenous injection of adrenalin and pituitary extracts.

4. The inhibitory factor of extracts of the suprarenal glands seem to disappear by decomposition, oxidation, or other process, before the blood-pressure raising element is gone. It would appear that the suprarenal and the pituitary bodies have at least one property other than those qualities generally recognized as present in them.

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THE CLINICAL VALUE OF THE QUANTITATIVE ESTIMATION OF PEPSIN.

WITH SPECIAL REFERENCE TO THE METTE AND RICIN METHODS.*

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Beaumont's famous experiments showed that the gastric juice, even outside the body, had an active solvent action on food, and this led Müller to suspect the presence in it of a substance acting like diastase on starch flour. Eberle, in 1834, found this principle to be present in the acid gastric mucus. Müller and Schwann found that this was true of acid extracts of the mucous membrane, but that neither acid nor extract alone had any activity. Subsequent research showed that this was a property of the gastric mucus or secretion and not of mucus in general, as was originally surmised. Pepsin has since that time been exhaustively studied, and many remarkable facts have been demonstrated, the most interesting of which is Schütz's law, so-called, which is that the quantity of pepsin varies according to the square of the amount of albumin digested. In spite of all the effort that has been devoted to its study, pepsin, as such, has never been isolated in a pure state, so that it is impossible to estimate it quantitatively in a true sense of the word; all that can be done is to measure its effects and thus gain an idea of its concentration in a given solution.

The numerous quantitative methods for the estimation of the activity of pepsin have been so frequently reviewed that it is hardly necessary to discuss the older literature at length in the present paper. It will be sufficient to refer to the summaries in recent text-books, such as that of Boas, or to the articles of Koettlitz, Nirenstein and Schiff, Robin, Roth, and others. The following brief enumeration is, in part, after Roth:

1. The procedures of Bidder and Schmidt, Brücke, Gruenhagen, Jaworski, and Herzen are methods in which the stomach contents are diluted until no further digestion occurs or in which a certain amount of albumin or fibrin is exposed to the digestive action of pepsin for vary-

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ing periods of time. The amount of pepsin is calculated with reference to the dilution required or the time elapsed. Grützner and Bourget used fibrin colored with carmin and estimated the amount of pepsin by the intensity of the red color of the gastric juice produced by the solution of the fibrin. Spriggs utilized the change in the viscosity produced by digestion as a measure of the ferment action. These methods at the best can only give approximate results.

2. Klug (Van Valzah and Nisbet) used the biuret test as a measure of the albumin digestion. The elder Schütz, Oppler and J. Schütz also calculated the amount of pepton formed; Schütz by the polarimetric method and Oppler and J. Schütz by the estimation of the total nitrogen. Oppler used the Kjeldahl method, but surrounded his test with so many precautions to secure natural conditions of ferment action and accuracy in results that it is generally regarded as the best and at the same time the least available of all methods.

3. In recent years Mette, Hammerschlag, Bettman and Schröder, Solms, Gross and others have introduced methods which aim at the exactness of the last-named procedure, combined with ease of application. Solms' test is described in full below. Bettman and Schröder determined the amount of pepsin by observing the rapidity with which the foam produced by shaking up an albumin solution containing pepsin is dissolved. Some of those who have employed this plan do not appear to have been favorably impressed (Cobb). Hammerschlag's method is too widely known to require detailed description. It is based on an estimation of the albumin in a special solution, before and after digestion, by means of the Esbach albuminometer. We have used it in a few cases and have found, as far as our limited experience goes, that the results correspond in a general way with those obtained by the Mette method.

The following table illustrates a few comparative tests with the Mette and Hammerschlag tests:

No.	Mette.	H.
M 498	4.3 mm.	97 per cent.
M 638	3.9 mm.	87 per cent.
M 505	3.2 mm.	81 per cent.

Hammerschlag's test is generally regarded as inferior to that of Mette and possesses many faults which have been enumerated by Roth and others.

The method of Mette, as modified by Nirenstein and Schiff, is generally conceded to compare in exactness with that of Oppler. The technic which we have employed is not widely different from that of Nirenstein and Schiff (cf. Sahli) and was described by one of us, with Dr. Sailer, a year or two ago. For the convenience of those to whom it is unfamiliar

it may be briefly described. Glass tubes, 1 to 2 mm. in caliber and 20 or 30 cm. in length, are filled by suction with white of egg, plugged with bread and boiled for five minutes. They are then sealed with sealing wax and after three days are ready for use. The test is carried out as follows: One c.c. of the gastric filtrate is diluted with 15 c.c. of N/20 hydrochloric acid. Two sections of tubing, 2 or 3 mm. in length, are added. A triangular file is sufficient for cutting the tubes. The specimen enclosed in a covered dish is kept in a thermostat at 37° C. for twenty-four hours. At the end of this period the column of albumin digested at each of the four exposed ends is carefully measured in tenths of a millimeter. An average of the four readings is recorded as the result, but it is usual to square this for comparison with other tests in accordance with Schütz's law.

The following examples will make this clear:

No.	Dil.	Reading.	Squares.	Relative Strength.
P.271	1 in 4	6.8	46	4
P.271	1 in 16	3.4	11.6	1
P.273	1 in 4	6.4	41	4 (approx.)
P.273	1 in 16	3.3	10.9	1

Mette's test thus modified excludes various errors which impair the value of many other methods, because it possesses the following advantages:

1. The acidity in all cases is rendered approximately uniform without any tedious titrations being required.

2. The dilution is sufficient to overcome inhibition due to albumoses (Sailer and Farr), etc., or antiferments.

3. A uniform surface is exposed to digestion at all times.

4. Numerous observations show that it complies with Schütz's law in dilutions sufficient to avoid inhibition and to prevent a digestion of more than 4 mm.

Objections to the method are:

1. Albumin from different eggs or albumin coagulated at different temperatures or heated for different periods of time varies considerably in digestibility.

2. Differences in the caliber of the tubes beyond certain limits affect the readings.

3. Wide variations in the temperature of the thermostat have the same effect.

4. There is a decided personal index in measuring the column of albumin.

These faults can be largely overcome by the following measures:

1. An unvarying technic and the use, possibly, of artificial or dried egg albumin of uniform quality (Onuf).

2. The use of an artificial pepsin control. For this purpose a 1 or 2 per cent. solution of a standard pepsin should be employed, diluted 1 in 16 in the same way as the specimens to be examined.

3. A uniform method of measurement.

In these tests we employed an ordinary clinical microscope (low power) fitted with a movable stage and vernier scale.

Two illustrations will show the value of controls where there are wide discrepancies:

(a) No.	Mette.
M 273	5.2
M 282	5.8
M 251	2.8
Control pepsin, 1/16 per cent.	4.2

(b) No.	Mette.
M 511	4.4
M 520	2.8
M 638	3.9
Control pepsin, 1-16 per cent.	2.8

Comparison in these cases leads us to lay less stress on the high figures obtained in the first experiment. Similarly M. 251 can be regarded as a case of greatly diminished pepsin, while M. 520 with the same reading is merely a low normal.

Jacoby, in 1906, in a short article disputing Pawlow's assertion that pepsin and rennin were identical, introduced a new method of determining pepsin, which, he claims, decided definitely the individuality of the two ferments. This method was by means of ricin, a solution of which, he found, was cleared up by pepsin. Although this peculiar property had been observed by him some time before while pursuing his study of ricin, its adaptability to clinical use was not brought forward until Solms published his paper in 1907.

Jacoby had found that, if pepsin were added to a 1 per cent. solution of ricin in salt solution, the cloudiness due to the albuminous substances in the ricin disappeared rapidly and completely. Working on this under Jacoby's direction, Solms evolved the following simple procedure, the only fluids needed being a solution of ricin and a N/10 hydrochloric acid solution:

The ricin solution is made by dissolving 0.5 gram of ricin in 50 c.c. of a 5 per cent. sodium chlorid solution and filtering. (The recin used by Solms was obtained from the Vereinigte chemische Werke, Charlottenburg, Salzufer 16, costing 2 marks for 10 grams. Solms preferred this preparation of ricin to Merck's, principally on account of the limited supply and the great cost of the latter.) The filtered ricin solution has a somewhat cloudy appearance, but on the addition of 0.5 c.c. N/10 hydrochloric acid solution becomes decidedly milky. The milky appearance is cleared up by pepsin.

His technic is as follows: The gastric juice is obtained by extracting the stomach contents one hour after the ingestion of an Ewald-Boas test breakfast. He tests this for the presence of free hydrochloric acid, then determines the total acidity, and in appropriate cases examines for lactic acid. According to his findings he makes varying dilutions of the contents with distilled water. In cases of hyperacidity he dilutes the filtered contents from 1:100 to 1:10000, whereas in cases of anacidity or subacidity the dilutions vary from 1:10 to 1:100. In normal cases he dilutes from 1:100 to 1:1000.

In each of the five test tubes he puts 2 c.c. of the filtered ricin solution; then with another graduated pipette he adds 0.5 c.c. N/10 hydrochloric acid, which causes the mixture to become very cloudy. Having numbered the test tubes 1, 2, 3, 4 and 5, he puts in the first tube 1 c.c. of boiled gastric juice; in the second, 0.9 c.c.; in the third, 0.8 c.c.; in the fourth, 0.5 c.c., and in the fifth, 0 c.c. Then he takes the unboiled juice and, having diluted 1 c.c. of juice with 99 c.c. of water, he puts in the first test tube 0 c.c.; in the second, 0.1 c.c.; in the third, 0.2 c.c.; in the fourth, 0.5 c.c., and in the fifth, 1 c.c., so that in each tube there are 3.5 c.c. of fluid. The test tubes are then corked and put in an incubator, where they are allowed to stand for three hours; at the end of this time they are taken out and the tubes examined to see with what dilution the ricin has been cleared up. If an incubator is not at hand the tubes can be left at room temperature, of course for a correspondingly longer time.

In order to obtain a convenient expression of the pepsin content of a gastric juice, he designates that amount of pepsin contained in 1 c.c. of a 1:100 dilution, which is capable of clearing up the ricin solution after three hours' standing in an incubator, as 100 pepsin units. This he has decided on as the normal standard, because after many examinations of specimens of normal acidity he found the ricin to be cleared up by 1 c.c. of a solution diluted 1:100. Solms considers the normal acidity to be 40 to 60, and anything above or below this to be hyperacidity or hypoacidity, and gives tables showing the pepsin content in these various conditions. His tables show no fixed relation between the acidity and the amount of pepsin, except in those cases in which the acidity is very low or the free hydrochloric acid entirely absent, under which conditions the pepsin will be found to be low also. Solms thinks that from a study of his tables he has learned nothing which would tend to show that the estimation of pepsin has a diagnostic or therapeutic value.

Witte studied this new method of Jacoby and Solms and recommends it strongly on acount of its simplicity and cheapness. The only modification he proposes is to add a dilution of 1:50, since in his experience

there have been cases where a dilution of 1:100 did not quite dissolve the ricin. His conclusions are about the same as those of Solms, namely, that the normal pepsin unit is between 100 and 200 and that there is but slight relation between the acidity and the amount of pepsin, except in cases of lowered acidity, in which the pepsin is likely to be lower. Witte made a few comparisons with the Mette method, but prefers the ricin procedure.

TABLE 1.—NORMAL ACIDITY—40-60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	40	0	100 not clear.	1.6 (2.6)	Carcinoma pylorus.*	F. S.
2	40	30	100-200	3.8 (14.4)	Hyperchlorhydria	M., 464
3	42	+	100	3.1 (9.6)	Chr. constipation	P., 335
4	43	+	Not made.	3.3 (10.9)	Hyperchlorhydria	P., 273
5	44	26	200	3.2 (10.2)	Gastro-enteroptosis	M., 505
6	48	10	100	4.9 (24)	Chloro-anemia	M., 311
7	50	18	10	3.9 (15.2)	Chr. gastritis	M., 570
8	50	30	200	4.4 (19.4)	Migraine—dilatation of stomach	M., 511
9	50	+	100 not clear.	0.5 (0.25)	Pyloric obstruction†	G. C.
10	50	+	Not made.	3.2 (10.2)	Constipation—nervous dyspepsia.	P., 300
11	50	—	Not made.	4.9 (24.0)	Chr. constipation	F. B.
12	54	34	100-200	4.3 (18.5)	Gastric neurosis	M., 434
13	54	36	100	Not made.	Tubercular enteritis	M., 659
14	56	24	100	Not made.	Cholecystitis	M., 884
15	58	30	100 not clear.	3.7 (13.7)	Hyperchlorhydria	M., 402
16	58	34	100	3.0 (9.0)	Neura-thenia—gastric neurosis	M., 449
17	60	45	100	5.2 (27.0)	Cholecystitis hyperchlorhydria	M., 791
18	60	+	100	5.0 (25.0)	Malnutrition—chr. pancreatitis(?)	S. C.
19	45	20	100	Not made.	Gastric neurosis	M., 663

* Without preliminary lavage. Lactic ac. —. Lower dilution of ricin not made.
† Probable carcinoma. Butyric acid. Lower dilution of ricin not made.

Gross advances a new method which he claims to be simpler than the foregoing. His method is based on the precipitation of undigested casein by sodium acetate, but we have had no opportunity of studying its value. Gross claims that the Jacoby-Solms method is open to criticism on one point, and that is that the ricin they used is very impure and that there is no way of determining just what foreign bodies are mixed with it. He also objects to the method on grounds of expense, but this, depending merely on a personal point of view, requires no comment.

In making our studies we have followed closely the technic as laid down by Solms and have seen no reason to make any change or modification. The only drawback we have encountered is that the ricin solution must be freshly prepared. We tried making up a large amount, and filtering it only as needed, but the filtrate was so cloudy that it was difficult to determine the extent of pepsin digestion, as the solution did not become clear even when the gastric juice was but little diluted. After the ricin solution is once made, the preparation of the five tubes for peptic digestion occupies very little time, not more than seven minutes on an average, when once the technic has been perfected.

The results of our studies are shown in the accompanying tables, which are self-explanatory.

SUMMARY OF THE TABLE OF NORMAL ACIDITY (40-60).

Apart from three cases, Nos. 1, 9 and 18, the ricin and the Mette methods gave results within normal limits. In our table the ricin results of Case 1 is reported as "100 not clear," but in this case, as in Case 9, lower dilutions than 1:100 were not made. Finding that 100 was not digested, we should have begun with a dilution of 1:10, when there would doubtless have been a low reading corresponding with that by the Mette method. Case 18 shows the Mette result to be at the extreme upper limit of the normal, while the ricin remains exactly normal. From a study of the table we see that, apart from those cases with organic acids or diminished free hydrochloric acid, no aid in diagnosis other than that derived from the ordinary chemical examination has been obtained by the determination of pepsin. In Case 9 retention, favoring the production of organic acids, is the cause of the relatively high acidity. The same case (Table 2, 10), after lavage, showed a very low acidity and a minimal amount of pepsin. Therapeutically, the table is suggestive, but nothing more.

SUMMARY OF THE TABLE OF LOW ACIDITY (BELOW 40).

With low acidity the pepsin is also low, both by the ricin and Mette methods. In two instances, Cases 8 and 5, the Mette was normal, while the ricin was absent or diminished, respectively. This discrepancy can be explained, as the controls for the Mette tests were also high. In Case 14 the ricin was normal, while the Mette was subnormal. We have no explanation to offer for this variation.

Pepsin determination seems to be of value in distinguishing simple gastritis and neuroses from achylia and carcinoma. In the last two the

pepsin is invariably very much diminished, whereas in the first two it is unaffected or but slightly altered. In this we disagree with Witte, who found that pepsin was always low in neuroses.

SUMMARY OF THE TABLE OF HYPERACIDITY (ABOVE 60).

With very few exceptions, the ricin and the Mette methods coincided in cases of hyperacidity, although the former is not capable of showing the finer gradations of the latter. In two cases, 27 and 55,

TABLE 2.—SUBNORMAL ACIDITY—BELOW 40.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	35	0	10-20	2.3 (5.3)	Endarteritis—chr. tuberculosis. . .	M., 140.
2	34	+	Not made.	3.4 (11.6)	Constipation—Subacidity.	P., 271.
3	28	6	10	2.8 (7.8)	Cholelithiasis gastritis	M., 251.
4	26	0	20-50	2.0 (4.0)	Polycythemia—chr. gastritis*. . . .	M., 814.
5	26	8	10-20	3.3 (10.9)	Gastric neurosis	M., 579.
6	25	0	10	0.8 (0.64)	Pyelitis	M., 189.
7	22	0	10	1.0 (1.0)	Chr. gastroenteritis†.	M., 813.
8	22	0	0	3.4 (11.6)	Chr. gastritis	M., 571.
9	20	0	0	0.1 (0.1)	Anacidity	M., 576.
10	12	0	Not made.	0.5 (0.25)	Carcinoma pylorus‡.	F. S.
11	12	0	Not made.	0.8 (0.64)	Chr. Diarrhea—achylia gastrica§. .	P., 350.
12	12	0	Not made.	0.5 (0.25)	Incipient tbc.—splanchnoptosis achylia gastrica	P., 15.
13	4	0	Not made.	0	Achylia gastrica‖	P., 270.
14	18 (1)	+	100-200	2.4 (5.7)	Spastic stricture of esophagus. . . .	P., 302
15	34 (2)	+	100 not clear.	2.2 (4.8)	ib**	ib.
16	6 (3)	0	10 not clear.	0	ib††	ib.

* Vomitus.
† Lactic acid present.
‡ Lactic acid present after lavage. See F. S., Table 1.
§ No lactic acid.
‖ Lactic acid present.
** Lower dilution of ricin not made.
†† Contents of esophageal dilatation.

the ricin was 1,000, while the Mette was also high. In Case 37 there was a disproportion between the two methods, the ricin being 1,000 while the Mette showed a normal value. In this case two dilutions of ricin were made, one of 1:100 and the other 1:1000, in each of which the result was 1,000 units. In two other cases, 53 and 56, the ricin was abnormally high and the Mette low, which can be explained by the low result obtained in the control experiment.

Here our efforts to find some diagnostic aid in the quantitative estimation of pepsin have met with failure. The fact that there is no definite relation between the degree of acidity and the amount of pepsin might suggest the use of artificial pepsin in occasional cases.

COMPLETE SUMMARY.

Our tests indicate that the normal variation of the Mette method is between 3 (9) and 5 (25), of the ricin method 100 to 200. In carcinoma ventriculi, achylia and occasionally in chronic gastritis, the pepsin determination reveals values below the minimal normal, but as a rule in neuroses and chronic gastritis the pepsin is relatively but little affected in contradistinction to carcinoma and achylia, and this would seem to be of assistance in making a differential diagnosis between these conditions. We have found, as have others, that within normal limits there are wide variations without apparent relation to the acidity, but at present we are not in a position to draw any diagnostic or therapeutic conclusions from these observations.

The results obtained with the ricin method correspond with those shown by the Mette method; that is, normal values and subnormal values are clearly shown, but the finer variations are not seen and when present frequently do not correspond with the Mette results. This is true even when we have made allowance for differences in the Mette tubes by means of the controls referred to above.

Both tests are valuable as rough quantitative methods, and they are carried out with equal facility. The Mette has the advantage of excluding variations due to differences in acidity without requiring any previous titration. There has been no attempt made to see whether the ricin method follows the law of Schütz, nor has there been any attempt made to bring the various tubes to a uniform acidity. The variation in the acidity of the five tubes would seem *a priori* to be fruitful of grave errors. This could probably be obviated by suitable dilutions with N/20 hydrochloric acid, similar to those employed by Nirenstein and Schiff in their modification of the Mette method. These questions may form the basis of a supplementary communication.

We have made little therapeutic use of the knowledge we have obtained. The wide variations in the pepsin values would suggest that the drug has been too much despised by stomach specialists, though this can not be said of practitioners in general. It would seem to be indicated in cases showing subnormal peptic values, with preservation of at least a fair degree of acidity. In chronic gastritis with low acidity and low pepsin, in achylia and in carcinoma it would be necessary to add hydro-

TABLE 3.—HYPERACIDITY—ABOVE 60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	62	+	Not made.	3.2 (10.2)	Gastric ulcer	P., 310
2	62	+	Not made.	3.8 (14.0)	Constipation—chronic gastritis	P., 229
3	62	+	100	4.6 (21.2)	Cholelithiasis—pyloric adhesions	P., 289
4	62	30	100-200	Not made.	Goiter—dilated stomach	M., 871
5	62	34	100	2.8 (7.8)	Psoriasis—eczema	M., 520
6	62	36	100-200	4.1 (16.8)	Gastric neurosis	M., 300
7	62	16	10	3.8 (14.4)	Carcinoma pylorus*	M., 227
8	64	40	100	3.3 (10.9)	Neurosis	M., 575
9	64	30	100	Not made.	Nephritis gastritis	M., 824
10	64	48	100	3.1 (9.6)	Adhesions(?)—hyperchlorhydria	M., 615
11	64	+	Not made.	2.3 (5.3)	Chronic gastro-enteritis	P., 272
12	65	40	100-200	3.6 (13.0)	Glycosuria	M., 500
13	65	40	100	3.4 (11.6)	Syphilis—neurasthenia	M., 176
14	66	40	100	2.8 (7.8)	Myalgia	M., 680
15	66	36	100	3.2 (10.2)	Tachycardia	M., 236
16	66	40	100	Not made.	Gastroptosis—gastric neurosis	M., 225
17	67	+	Not made.	3.4 (11.6)	Epilepsy	P., 324
18	68	24	200	3.6 (13.0)	Frontal sinusitis—neurosis—hyperacid.	M., 423
19	68	42	200	4.3 (18.5)	Gout—neurosis—alcoholic gastritis.†	M., 498
20	68	34	100 not clear.	3.3 (10.9)	Pancreatitis—hyperchlorhydria	M., 356
21	68	46	100-200	4.6 (21.2)	Cholecystitis gastric ulcer	M., 322
22	68	+	100	4.0 (16.0)	Hypochondriasis	F. W.
23	68	+	Not made.	3.2 (10.2)	Gastric ulcer	F. M.
24	68	44	100-200	5.9 (34.8)	Chr. appendicitis—gastric neurosis	M., 757
25	70	40	100	Not made.	Jaundice—cholecystitis	M., 664
26	70	40	100-200	4.0 (16.0)	Gastritis—hyperchlorhydria	M., 734
27	70	54	1000	5.8 (33.6)	Hour-glass contraction of stomach—pyloric adhesions.	M., 282
28	70	46	100	3.2 (10.2)	Fibroid of uterus—hyperchlorhydria	M., 371
29	73	+	Not made.	4.4 (19.4)	Constipation—hyperchlorhydria	P., 258
30	74	44	100	4.7 (22.0)	Hyperchlorhydria—pylorospasm—cholecytitis—chr. appendicitis.	M., 335
31	75	55	100	3.0 (9.0)	Hyperchlorhydria	M., 538
32	75	40	100-200	3.0 (9.0)	Exophthalmic goiter	M., 455
23	76	30	100	4.0 (16.0)	Appendicitis	M., 326
34	76	+	Not made.	3.0 (9.0)	Splanchnoptosis	S P.
35	76	+	Not made.	5.4 (29.1)	Gastroptosis—hyperchlorhydria	P., 193

* Vomitus.

† Hammerschlag, 97%.

TABLE 3.—CONTINUED.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
36	78	56	100	3.5 (12.3)	Chr. appendicitis	M., 593
37	78	64	1000	3.8 (14.4)	Appendicitis—hyperchlorhydria.‡	M., 476
38	78	36	100	3.9 (15.2)	Hyperchlorhydria	M., 450
39	78	40	100	3.8 (14.4)	Gastric ulcer	M., 430
40	80	+	Not made.	4.0 (16.0)	Splanchnoptosis—incipient tbc.	P., 296
41	80	55	100	3.4 (11.6)	Hyperchlorhydria	M., 678
42	80	55	100	3 0 (9.0)	Hyperchlorhydria	M., 585
43	82	52	100	3.0 (9 0)	Hyperchlorhydria	T. T. M.
44	82	52	100	3.8 (14.4)	Bronchitis—gastritis	M., 599
45	82	+	100	4 6 (21.2)	Cholelithiasis—hyperchlorhydria	F. B.
46	82	54	100	3.4 (11.6)	Gastritis	M., 689
47	84	52	100	3.1 (9.6)	Hyperchlorhydria	T. M. B.
48	84	60	100	Not made.	Neurosis—hyperchlorhydria	M., 883
49	85	35	100	2.9 (8.4)	Neurasthenia—gastroptosis	M., 692
50	85	55	100	2.6 (6.8)	Gastric neurosis	M., 667
51	86	48	100	4.9 (24.0)	Gastric neurosis	M., 561
52	86	58	100	5.2 (27.0)	Appendicitis—hyperchlorhydria	M., 273
53	88	54	500	2.8 (7.8)	Cholecystitis—hyperchlorhydria.§	M., 171
54	88	58	100-200	4.9 (24.0)	Frontal and ethmoidal sinusitis—hyperacidity.	M., 785
55	88	62	1000	5.3 (28.0)	Gastritis—hyperchlorhydria°	M., 334
56	95	60	500	3.1 (9.6)	Neurosis—hyperchlorhydria	M., 489
57	100	45	100	2.9 (8.4)	Gastric ulcer	M., 597
58	106	94	100-200	Not made.	Cystitis—enteritis	M., 828
59	110	62	200	3.7 (13.7)	Epilepsy(?)	M., 713
60	112	+	Not made.	4.2 (17.6)	Hyperchlorhydria	P., 341

‡ Two controls, first with dil. of 1:100; second with dil. of 1:1000.
§ Mette control also low.

chloric acid. In many cases it is doubtful if enough acid could be introduced, except occasionally with a stomach tube, to allow of normal proteolysis. A practical expedient (Sailer) is to saturate meat or milk, before taking, with dilute hydrochloric acid until free acid can be detected, after which a small dose of hydrochloric acid will suffice. Pepsin should be given in sufficient amounts to make a 1/4 to 1/16 per cent. solution in the contents of the stomach (estimated in advance). It should be given with or followed by at least twenty minims of dilute hydrochloric acid. Both may be repeated once or twice at short intervals to make up

for the amount expelled into the duodenum. Gasterine, or the normal gastric secretion of the dog obtained through a Pawlow fistula, has been advocated by Frémont and others (see Bettmann) in doses of 100 to 500 c.c. We have had no experience with it, but it would seem to have no advantage over a mixture of pepsin and hydrochloric acid unless it possesses some "vital" or other property independent of its principal constituents.

In conclusion, we desire to acknowledge our indebtness to Drs. Musser, Sailer and Talley for the use of their clinical material, which we have freely used to supplement our own.

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